Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study

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Abstract: Background
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Methods
We analysed data on more than two million rare cancer diagnoses, provided by 83 cancer registries, to estimate European incidence and survival in 2000-2007 and the corresponding time trends during 1995-2007. Incidence rates were calculated as the number of new cases divided by the corresponding total person years in the population. Five-year relative survival (RS) was calculated by the Ederer-2 method. Seven registries (Belgium, Bulgaria, Finland, Ireland, Netherlands, Slovenia, and the Navarra region in Spain) provided additional data on hospitals of treatment for about 220,000 cases diagnosed in 2000-2007. Hospital volume was calculated as the number of treatments provided by each hospital rare cancer group sharing the same referral pattern.
Findings
Rare cancers accounted for 24% of all cancers diagnosed in EU28 during 2000-2007. The overall incidence rose yearly by 2.3%. RS increased (overall 5.7%), from 1999-2001 to 2007-2009, and for the majority of rare cancers, with the largest increases for hematological tumors and sarcomas. The level of centralization of rare cancer treatment varied

widely between cancers and between countries. The Netherlands and Slovenia had the highest treatment volumes.

Interpretation

The study profits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments and better case management. There is ample room for improving the centralization of treatment in these seven European countries.

The research was funded by the European Commission (Chafea) [Grant No. 2000111201].

Burden, time trends and centralized treatment of rare tumors: a European perspective. The RARECAREnet population-based Project

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Summary

Background

Rare cancers here defined as those with an annual incidence rate less than 6/100,000 in Europe, pose challenges for diagnosis, treatments, and clinical decision-making. Information on rare cancers is scant. We updated the estimates of the burden of rare cancers in Europe, their time trends in incidence and survival, and provide information on centralization of treatments in seven European countries.

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The study profits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments and better case management. There is ample room for improving the centralization of treatment in these seven European countries.

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Introduction

The RARECARE project defined rare cancers as those with an annual incidence rate less than 6/100,000 in Europe (EU), and showed that about one in five were rare types and slightly more than four million rare cancers were prevalent in the EU population [1]. Because of their low numbers, the almost 200 rare cancers listed by RARECARE pose challenges for diagnosis, treatments, and clinical decision-making. Clinical trials are rare too, and it is hard to build up new knowledge and expertise.

There is a broad consensus that the diagnostic pathologic confirmation and primary treatment of rare cancers, in particular, should be centralized in reference centers and/or in collaborative networks, with multidisciplinary approaches [2] and very specific expertise. In addition, clinical and translational research calls for a high level of centralization and international collaboration. To what extent appropriate policies for rare cancer patients are implemented at the country level has

seldom been studied. As a consequence, information for policy makers and stakeholders is scarce for many of these tumors.

The project Information Network on Rare Cancers (RARECAREnet) is designed to update epidemiological information on rare cancers in the EU [3], to provide indicators at the country level, time trends, and to study to what extent treatment is centralized in Europe.

This paper provides up-to-date incidence and survival estimates based on data collected from 94 population-based cancer registries (CRs), for 198 rare cancers diagnosed in 2000-2007 and for 12 major families of rare cancers. It also presents data on the levels of centralization for rare cancers in selected European countries.

Material and Methods

Patients

The data were extracted from two databases. The first, the descriptive analysis database, is a subset of the EUROCARE-5 database [4]. It includes incidence and follow-up data provided by European population-based CRs regarding cancer patients diagnosed in the period Jan 1,1978 to Dec 31, 2007. Vital status was updated to Dec 31, 2008. From the 117 CRs participating in EUROCARE-5, we excluded specialized pediatric CRs, the Swedish and Turin CRs, because they did not participate in the RARECAREnet study, and the Danish CR, because it provided none of the details on morphology needed to define rare cancers. Details of the RARECAREnet database can be found in the report on the project website [5]. For the analysis of incidence we excluded 11 CRs specialized in specific anatomical sites to avoid incomplete coverage of some cancer entities affecting multiple sites such as neuroendocrine tumors. A total of 1,984,147 rare cancer diagnoses were considered for incidence estimates in 2000-2007, collected by 83 CRs from 1,566 million person-years of observation. Data for incidence trends came from 42 CRs covering the period 1995-2007, and included 2,268,602 cases, and 1,900 million person-years of observation. Survival estimates in 2000-2007 for all the rare cancers were based on a total of

1,994,346 diagnoses, observed by 94 CRs. Case identified only with death certificate (DCO) or casually discovered at autopsy were excluded from the analysis because they do not report time of survival. Cases lost to follow-up were considered as censored at the date of last contact. Multiple primaries in a same patient were included. Death certificate only (DCO) and autopsy cases were excluded but data included multiple primaries in a single patient. Finally, survival trend analysis was based on 1,649,309 rare cancer diagnoses from 45 CRs providing uninterrupted data from at least Jan 1, 1995 to Dec 31, 2007.

The second database was used for the study of hospitals of treatment and hospital volume. It comes from seven European CRs: the national CRs of Belgium, Bulgaria, Finland, Ireland, Netherlands, Slovenia, and the regional CR of Navarra (Spain). This last, although regional, was added in consideration of the regional organization of the Spanish health care system. These CRs were selected to reflect the variability of incidence and survival in Europe [1,5], and because they could provide detailed data for all 198 rare cancers. Variables included: sex, dates of birth and diagnosis, topography and morphology codes, from the International Classification of Disease for Oncology version 3 (ICDO-3) grading, pathological and clinical TNM, simplified stage (localized, regional extension, metastatic), treatment (surgery, radiotherapy, systemic, other or none), vital status, date of closure of follow-up or death, hospital of diagnosis and hospital of treatment. DCO and autopsy cases (1.3% overall, with a maximum of 8.6% in Bulgaria) were not included. The hospital of diagnosis was defined as the hospital where the pathology examination was done or requested. The hospital of treatment(s) was defined as the hospital where a specific treatment (e.g. surgery) or the first course of systemic therapy (e.g. chemotherapy) was given. Up to five different types of treatment within one year from the date of diagnosis were considered as a primary treatment. Vital status was further updated, with respect to the descriptive analysis database, to Dec 31, 2012.

We received data on about 348,000 rare cancers diagnosed in the period 2000-2007. However, national data from Belgium were limited to the period of diagnosis 2004-2007, and those from Navarra to 2000-2005. Cases diagnosed in Bulgaria and the Netherlands during 2000-2004 were removed on account of incomplete national coverage of hospital information. A total of 223,081 rare cancer cases were included in the hospital volume study database. Unspecific morphologies (8000, 8001, 8010, 8800, 9800, 9590) were found in 2.1% of cases, with the highest proportion (4.1%) in Finland. Seventeen per cent of cases (37,959/223,081) was removed, because for them the information of hospital was missing.

Methods

Rationale of the definition of rare cancer entities and their classification in terms of ICD-O codes are reported elsewhere [1,2,5]. Classification was structured in way to avoid any overlapping among rare entities. For example, GEP NET and GIST tumours were under the families of NET and sarcomas, and not also in digestive rare cancers.

Incidence rates were estimated as the number of new cases arising in 2000-2007 divided by the corresponding total person years (male + female) in the general population. The European standard population was used for direct age standardization. New cases in 2013 in EU28 were calculated by multiplying age- and sex-specific incidence rates in 2000-2007 by the corresponding European population classified in five-year age classes on 1 January 2013.

Incidence variation over time was estimated restricting the analysis to 1,480,424 cases diagnosed in the two sub-periods 1999-2002 and 2003-07, and was presented in a funnel plot where each dot represents a single rare cancer, the y-axis displays the estimated difference in terms of annual percent change (APC) of age-adjusted incidence, and the x-axis the corresponding precision in terms of the inverse of its standard error. APC was calculated as the ratio between incidence rates for the two sub-periods elevated to 1/4.5, the inverse of their mean time distance. Three-standard-deviation confidence intervals for estimated zero changes [6] are represented by

two symmetrical lines progressively approaching the x-axis with increasing x values. Dots lying above or below the area between them correspond respectively to tumors with 99.8% significantly higher or lower incidence rates.

Five-year relative survival (RS) was estimated as the ratio of observed to expected survival in the general population, matched by age, sex, calendar year, and geographical area, and calculated by the Ederer-2 method [7]. RS time trends were estimated by the period approach considering three follow-up periods: 1999-2001 (cohorts diagnosed in Jan 1,1995 to Dec 31, 2001), 2002-04 (cohorts diagnosed in Jan 1,1998 to Dec 31, 2004), and 2005-07 (cohorts diagnosed in Jan 1, 2001 to Dec 31, 2007). RS changes were presented as a funnel plot, similarly to incidence changes, but using the difference between five-year RS in the last and first of these periods on the y-axis.

The volume (number) of treatments provided by each hospital was calculated for major cancer groups, defined by aggregating all the solid rare cancers into 38 groups sharing the same referral pattern (see Figure 3). For example, all the 17 head and neck tumors, identified [1] as clinically distinct rare entities, are usually referred to head and neck specialized services, and were considered as a single group. Hematological rare tumors, not always requiring hospitalization, were not considered in the volume analysis. Hospital volume for each of the 38 groups was then computed as the annual number of *any* treatment delivered by the hospital, for all the cancers in that group. Repeated admissions to the same hospital for the same cancer and the same treatment type (i.e. surgery, radiotherapy or systemic therapy) were considered as a single admission and counted as one treatment in the analyses. Instead, repeated admissions for several treatment types (such as radiotherapy and subsequent surgery) given to a patient in the same hospital were all counted as treatments. Untreated patients were assigned to the hospital of diagnosis. The total number of treatments provided by each hospital for a given group of rare

cancers was then divided by the number of years of observation to provide its mean annual hospital volume.

Finally, for each patient we calculated the mean annual volume of the hospital(s) where they were treated, so obtaining a patient-specific measure with a much less skewed distribution with respect to the hospital-specific volume. Averaging this measure over all the patients diagnosed with a given group of rare cancers in a certain country gives a cancer- and country-specific measure of the level of expertise that patients can expect for the treatment of their tumor. We called it the *mean admission volume* (MAV) indicator.

Role of the funding source

The funders had no role in study design, collection, analysis or interpretation of data, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Burden of rare cancers in Europe

Table 1 provides incidence and survival estimates for each of the 198 rare cancers, for 63 groups of rare cancers (capital letters), for the 12 wider families in which rare cancers are hierarchically grouped, and for six common cancer groups. Hematological malignancies, rare cancers of female genital organs and of the digestive tract, and head and neck cancers were families with the highest overall incidence rates (from 15 to 28/100,000/year). Thoracic cancers, male genital and urological, endocrine organs, central nervous system (CNS) tumors and sarcomas had overall incidence rates from 5 to 8/100,000. Rare skin cancers and non-cutaneous melanoma, and embryonal cancers were the families with the lowest rates (1.22 and 0.34 per 100,000). Overall, rare cancers accounted for 24% of all cancers diagnosed in EU28 during 2000-2007; by far the majority were solid cancers (76%). For sex-specific rare cancers, we also provide in supplementary table (see appendix p 1) sex specific incidence rates.

Five-year RS of all rare cancers together was 49%, compared to 63% for all common cancers. Rare cancers also had lower survival within the families of digestive cancers (15% *vs.* 41%), female genital cancers (58% *vs.* 82%), male genital and urologic cancers (74% *vs.* 76%), skin cancers (70% *vs.* 96%) and hematological tumors (51% *vs.* 61%). The only exception was the group of thoracic cancers (13% *vs.* 10%), where common cancers included squamous cell carcinoma of the lung - with a very bad prognosis (6% after five years). Families including only rare cancers had five-year RS ranging from high, as for embryonal and endocrine organ tumors (79% and 88%), to intermediate, for sarcomas (60%), neuroendocrine (54%) and head & neck tumors (52%), and low for CNS tumors (21%).

Time trends of incidence and survival for rare cancers are shown in Figures 1 and 2. Cancers whose incidence variation fell outside the confidence interval shown in Figure 1 are listed in Table 2, with the age-standardized incidence estimates for 1999-2002 and 2003-2007, the corresponding APC and three-standard-error confidence intervals. Rare cancer dots in the plot seem to be distributed fairly symmetrically around the zero-change line, indicating no major systematic shifts in incidence. Overall there was a slight increase: the average APC for all the entities was +2.3% per year. There was a significant increase in incidence (99.8%) for 16 rare cancers, and a significant decrease for ten. Trends of rare cancers did not substantially differ from those of common cancers (data not shown), whose average annual change was +0.9%. Only prostate and skin cancers had an APC greater than 2%, while only epithelial cancers of the stomach decreased more than 2%.

Survival increased from 1999-2001 to 2005-2007 for the majority of rare cancers. The cloud of points in Figure 2 is skewed upward from the zero line, corresponding to a mean increase in survival, averaged over all the entities, of about 5.7 percent points. Twenty-four rare cancers presented significant survival increases (Table 3), while only one (other myelodysplastic syndromes) had a slight but significant decrease. Rare cancers with the largest survival increases

were mainly hematological: chronic myeloid leukemia, diffuse B cell lymphoma, follicular lymphoma, precursor B/T lymphoblastic leukemia/lymphoma, and multiple myeloma. Well represented among the top tumors with increasing survival were sarcomas, specifically of the viscera, trunk, and Kaposi sarcoma. Survival increases higher than five percent points were also observed for infiltrating ductal carcinoma of the prostate (12 percent points), poorly differentiated endocrine carcinoma of the digestive system (7.5 percent points), and squamous cell carcinoma of the oropharynx (7.1 percent points). There were no major improvements for rare cancers of the colon, rectum, breast and kidney, differently from the corresponding groups of common cancers [8].

Where are rare cancers treated?

Figure 3 illustrates the extent of centralization of rare cancer treatment, presenting MAV, overall and by country, for 38 cancer groups ranked by decreasing incidence. Logarithmic scale is here used for the x-axis to made the graph readable despite the huge MAV variability (from 82 to 0.2 per year) across the considered cancers. A supplementary Table (see appendix p 3) gives the numbers for the graphs. Pooled MAV (Figure 3a) ranged from a maximum of 83 treatments per year for head and neck tumors to fewer than 0.5 per year for choriocarcinoma of the placenta, some embryonal and endocrine tumors. The higher the incidence, the larger the MAV of treating hospitals. The relationship between cancer incidence and MAV in the pool of countries was very strong (Pearson coefficient 0.88), though with several outliers. This was the case for epithelial tumors of the ovary, which had a higher incidence but a lower MAV than CNS tumors, whose patients seemed therefore to be more centralized than ovarian cancer patients (35 *vs.* 20 cases treated per year). Similarly, soft tissue sarcomas had a five times higher incidence, but received less centralized treatment than bone sarcomas. Treatment for for thyroid cancers, uveal melanoma and several embryonal tumors appeared to be fairly concentrated in few hospitals with

relatively high volumes. In contrast, tumors of the urinary tract, gastro-entero-pancreatic neuroendocrine tumors (GEP-NET), small intestine, non-epithelial ovary cancers, and NET of skin were treated in centers with an even lower MAV than would be expected because of their very low occurrence.

With some exceptions, country-specific patterns of MAV reflected the overall picture. Differently from what found in the other countries, the management of epithelial ovarian cancers was highly centralised In Bulgaria and Slovenia. CNS patients were treated in highly centralized structures in all countries except Finland and Navarra. Treatment for uveal melanoma and retinoblastoma was not centralized in Bulgaria and, again, in Navarra. Slovenia and the Netherlands had the highest centralization patterns, while MAV for the majority of cancers was very low in Navarra.

Table 4 presents, for each country and 29 rare cancers, the annual number of cases diagnosed, the number of top-volume hospitals treating at least 75% of national cases, and the average annual numbers of treatments provided. Taking for example head and neck cancers, 3/4 of patients were centralized in two top hospitals in Slovenia (2 million population, 266 treatments per hospital per year), and 12 top hospitals in the Netherlands (17 million population, 201 treatments per hospital per year). The level of centralization was lower in the other countries, resulting in a caseload of 145 in the ten Bulgarian top hospitals, 106 in the 29 Belgian hospitals, and respectively 83, 77, and 63 in Finland, Navarra and Ireland. The Netherlands and Slovenia had the highest treatment volumes out of the 29 considered, with 12 rare cancers each.

Discussion

Rare cancers make up one quarter of all malignancies. They are a very heterogeneous group of almost 200 cancers, mostly solid, constituting from 2% of all skin cancers up to 32% of all female genital cancers. We confirmed the lower five-year survival for rare than common cancers (49% *vs.* 63%), and for all cancer families except thoracic cancers. The disadvantage persisted even

after excluding common cancers with good prognosis, of prostate, breast and skin. Several factors help explain these differences: the biology of the diseases, adequacies of diagnosis and treatment, lack of effective therapies, or lack of evidence-based treatment guidelines.

A novelty of this study is the analysis of incidence and survival trends. Overall, incidence rose by 2.3% a year from 1999 up to 2007. The increase was substantial for several rare cancers (Figure 1). Some of the increase can probably be attributed to improvement in pathological diagnosis, new entity codes in the ICD-O-3 and to the time needed to adapt the coding procedures. This is the case of GIST, large cell carcinoma of the lung, neuroendocrine tumours and many hematological codes [9-11]. For other rare cancers, increases in incidence may be due to better pathological diagnosis, like for the neuroendocrine tumors. For thyroid carcinoma several authors have suggested an increase in over-diagnosis [12]. However, increased exposure to risk factors may explain higher incidence rates for oropharynx and anal canal squamous cell cancers due to human papillomavirus (HPV) [13,14] and for adenocarcinoma of the esophagus, perhaps due to increasing obesity or gastro-esophageal reflux [15]. The lower squamous cell carcinoma cervix incidence might reflect organised cervical screening programs. The drop in incidence for some of the rare cancers was due to the still falling prevalence [16] of smoking .

RS improved by about 3% overall, slightly less than for common cancers (5.5%, data not shown), suggesting that investments were more focused on these latter. Also, over-diagnosis is expected to affect more common than rare cancers. Success was greatest for chronic myeloid leukemia (CML) with a five-year gain in survival of 21% across the study years, largely explained by the widespread use of new and more effective treatments, such as targeted treatments and more effective stem-cell transplantation [17]. For many other hematological cancers, new (targeted) drugs, combination with radiotherapy and again improvement in transplantation are responsible for the impact on prognosis [18]. Survival also improved for some groups of sarcoma (viscera,

trunk and limbs) for which multidisciplinary approaches and centralization of treatments may take the credit. This may also be true for neuroendocrine tumors [19], biliary tract, liver [20] and esophageal cancers [15], for which there are now more specific and effective treatments/protocols. For esophageal cancers, earlier detection through Barrett's esophagus surveillance practices might also contribute. For oropharyngeal cancers, the larger proportion of less aggressive tumors attributed to HPV may have influenced the survival gain [21]. For carcinoma of the thyroid and infiltrating ductal carcinoma of the prostate, early diagnosis should be the major factor. This would also have contributed to a rise in the proportion of cases that are clinically irrelevant, though this is hard to estimate [12, 22]. As found for incidence, some of the apparent survival gains may be due to classification changes [9], such as for large cell carcinomas of the lung.

Myeloproliferative neoplasms and myelodysplastic syndromes were not considered cancers until the WHO classification was changed in 2001, and their registration started even later [9]. More in general, the increases in incidence of some rare cancers could be due to more specific diagnosis and coding by registry.

The hospital volume analysis represents the first attempt to systematically study the place of treatment of rare cancers from population-based CR data. Many potentially relevant indications can be drawn from this seldom used source of information. However, several important limitations must be recognized. Seven CRs cannot be considered as statistically representative of the whole European population. Bulgaria, Finland and Navarra only provided information on, at most, three treatments: the first surgical, systemic and radiotherapy treatments. However, we estimated from the data of the other CRs that this problem only regard about 1% of all patients.

The mean admission volume estimates, based on individual patient data and blind administrative coding of hospitals, will depend on how cancer services were organized and coded. We cannot know if, for some rare cancers and in some countries, hospitals were linked in organized

networks during the study period, thus overcoming an apparent dispersion of treating structures. For example, patients with localised sarcomas or head and neck cancers were more frequently treated by small and/or peripheral hospitals [23]. If several hospitals provided different services but acted co-operatively as a single specialist center, their estimated volume will depend on whether they were identified as a single or separate units. Our data do not allow identifying in detail specific protocols used in the considered hospitals. Hospital volume can be therefore considered as an only partial quality indicator, mainly pointing to level of experience in protocol application and general management of rare cancer patients.

There are several suggestions that centralization of care improves outcome for rare cancers [24]. This is particularly true when optimal treatment requires complex surgery or high-technology radiotherapy equipment. It is beyond the scope of this paper to address the volume-survival relationship. Diagnosis and treatment in reference centers are expected to be more accurate because they benefit from large numbers of cases, which are often discussed in a multidisciplinary setting involving expert professionals. Often centralized sites are connected to research centers participating in international debates and research. Disadvantages of centralization are the need for patients to move and the risk of a longer waiting list, with consequent discomfort and possible negative effects on outcome [25].

Sometimes, centralisation was only moderately perceived by oncologists as a solution to be endorsed for rare cancer patients.[26]

For many of the solid rare cancers, centralization did not seem to have been completely achieved during the study period. However, most cases had been diagnosed more than ten years ago when centralization for cancer patients did not necessarily have much priority. Centralization seemed to be more widely implemented for rare cancers requiring highly specific technologies

(particularly radiotherapy and nuclear medicine) and for those with long-established evidence-based guidelines for diagnosis and treatment.

This was the case for many pediatric tumors, uveal melanoma, anal canal cancers, adrenal cortex cancers and, for specific surgical expertise, in CNS cancers and bone sarcomas.

The degrees of centralization varied across Europe, and to a large extent were affected by the population size. In countries with a small population it is easier to concentrate patients in a single or few hospitals. High admission volumes are more likely to be achieved in reference centers in larger-population countries.

The results of this part of the study were discussed in the participating countries at dedicated meetings attended by public health planners, oncologists, surgeons, representatives of Ministries of Health and patient associations. While the general pattern of dispersion was recognised, almost all the countries were working at different levels to implement centralization and/or network-based organizations for treatment, while still following country-specific priorities [27].

In Belgium, where all cancer patients can be treated in any hospital with an oncology care program, the level of centralization was low. A plan is now under way for the development of hospital networks between centers of expertise and other oncology care services/programs. Centralization was already ongoing in the Netherlands, mostly for surgical treatment. This was reflected in the high admission volumes in this country for many rare cancers (see appendix p 1).

In Bulgaria rare cancer patients were operated in all hospitals with surgical departments, while radiotherapy was concentrated in 17 centers and systemic therapy in 14 oncological hospitals. A major issue remains the quality of diagnosis, mainly due to inadequate facilities to diagnose many complex rare cancers. The definition of national and international pathways for second opinions from expert pathologists was deemed important. With this in mind, the European Reference Networks should offer a good opportunity to improve pathologist training through dedicated

training schemes and fellowships across Europe. Cancer registration remains vital for monitoring progress in rare cancer diagnosis and treatment for these patients.

In Finland, more than 60% of rare cancer patients were treated in five university hospitals. Centralization in single national structures was only observed for uveal melanoma and retinoblastoma. Further centralization for other rare cancers is impeded by the spread of the population over large areas and by administrative constraints on regional health authorities for referring cancer patients to the closest university hospital.

Irish public health authorities, during the period covered by the study, identified, a few centers to treat rare or particularly complex cancers. However, patients were not always correctly referred to them. This highlights the need for strong political commitment to ensure centralization, to make sure all rare cancer patients receive the highest quality of care.

Cancer care was highly centralized in Slovenia. In addition, the major hospitals were organized on a task-specific basis: radiotherapy was only provided by the National Cancer Center, while surgical treatment was more often done in two other major hospitals. Reducing delays in diagnosis and treatment was recognized in Slovenia as one of the major challenges in order to improve rare cancer outcomes.

Navarra is a relatively small region of Spain, a country with a highly regionalized health organisation. No hospital with national recruitment for rare cancers was operating in Navarra, and 98% of resident rare cancer patients were treated locally, the majority in the two largest regional hospitals. However, the admission volumes of Navarra hospitals are much lower than in all the other participating countries, even considering some underestimation due to unregistered patients coming from outside the region. This suggests some disadvantages in organizing rare cancer treatment on a regional/local basis.

To conclude, this is the largest study that estimates the burden of rare cancer for Europe, including trends in incidence and survival rates. It also provides indicators of rare cancer

treatment management. In seven European countries we observed - with few exceptions - a low level of centralization of treatment for rare cancers. We recognise the importance of population-based cancer registries in descriptive studies like this, to ensure surveillance. However, the quality of the data needs to be improved when morphology, hospital and treatment definitions are considered. To this aim, the use of specific data quality indicators, the planning of periodic sample-based quality studies and, above all, a wider use of these variables in population based studies, with related sensitivity analysis, can be suggested. Furthermore, the international classification for cancer have to rapidly include the new entities based on molecular and genomic categorization. The latter is a necessary condition for updating a new rare cancers list.

The European network of cancer registries (ENCR) should work to boost these quality improvements and make wider use of the data on rare cancers. The Joint Action of Rare Cancers [28] and the European Network for Rare Diseases will profit from these data, which are also useful for national and European policies to organize care for rare cancer patients better. The RARECAREnet project website includes a search tool with data for all the countries that contributed data [3].

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Author contributions

GG, RC and AT designed the study, and wrote the article. RC, LB, SM and RD did the statistical analyses. LB, RD, SM, EA, HC,ND, MKL, SS, JMVZ, LVE, OV, MPZ, LAA, FB, KI,RO and CSA revised the paper and contributed to data interpretation. All authors reviewed and approved the final version. Members of the working group collected data.

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Table 1. Estimates of incidence and survival for rare and common cancers, together with expected number of new cases

	Family	Cancer entity	Crude Incidence Rate per 100,000 per year	95% Confidence Interval lower	upper	Number of observed cases in 83 CRs in 2000-2007	Estimated new cases at 2013 in EU (28)	Five-year relative survival (%)	95% Confidence Interval lower	upper	Number of observed cases in 94 CRs in 2000-2007
RARE CANCERS											
	Head and neck cancers		18.82	16.76	16.89	263,565	84,989	52.1	51.8	52.3	254,563
		EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	0.45	0.44	0.46	7,046	2,282	47.3	45.8	48.8	6,867
		Squamous cell carcinoma with variants of nasal cavity and sinuses	0.35	0.34	0.36	5,465	1,770	49.5	47.8	51.2	5,444
		Lymphoepithelial carcinoma of nasal cavity and sinuses	0.00	0.00	0.00	31	10	70.8	50.7	99.0	31
		Undifferentiated carcinoma of nasal cavity and sinuses	0.02	0.02	0.02	286	93	30.5	24.3	38.2	283
		Intestinal type adenocarcinoma of nasal cavity and sinuses	0.00	0.00	0.00	42	14	65.0	48.9	86.4	42
		EPITHELIAL TUMOURS OF NASOPHARYNX	0.47	0.46	0.49	7,439	2,580	48.9	47.5	50.2	7,276
		Squamous cell carcinoma with variants of nasopharynx	0.36	0.35	0.37	5,613	1,941	48.5	47.0	50.1	5,589
		Papillary adenocarcinoma of nasopharynx	0.00	0.00	0.00	17	6	58.7	36.2	95.3	17
		EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	1.39	1.37	1.41	21,794	7,059	62.8	62.0	63.7	21,364
		Epithelial tumours of major salivary glands	0.96	0.95	0.98	15,053	4,876	60.8	59.8	61.8	14,703
		Salivary gland type tumours of head and neck	0.43	0.42	0.44	6,741	2,183	67.1	65.7	68.6	6,683
		EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	6.33	6.29	6.37	99,176	31,545	52.0	51.6	52.4	96,793
		Squamous cell carcinoma with variants of hypopharynx	1.27	1.25	1.28	19,828	6,422	25.1	24.4	25.9	19,878
		Squamous cell carcinoma with variants of larynx	4.61	4.58	4.64	72,210	23,389	60.5	60.1	61.0	71,928
		EPITHELIAL TUMOURS OF OROPHARYNX	3.32	3.29	3.35	52,017	16,848	40.9	40.4	41.4	50,843
		Squamous cell carcinoma with variants of oropharynx	3.12	3.09	3.14	48,812	15,810	41.3	40.8	41.8	48,401
		EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	4.78	4.75	4.81	74,890	24,257	56.7	56.2	57.1	73,101
		Squamous cell carcinoma with variants of oral cavity	3.51	3.48	3.54	54,931	17,792	48.0	47.5	48.6	54,229
		Squamous cell carcinoma with variants of lip	1.02	1.00	1.04	15,984	5,177	89.5	88.5	90.5	15,899
		EPITHELIAL TUMOURS OF EYE AND ADNEXA	0.04	0.04	0.05	679	247	80.6	75.9	85.6	673
		Squamous cell carcinoma with variants of eye and adnexa	0.03	0.02	0.03	421	136	88.9	83.0	95.2	422
		Adenocarcinoma with variants of eye and adnexa	0.01	0.01	0.01	134	43	58.7	49.1	70.1	134
		EPITHELIAL TUMOURS OF MIDDLE EAR	0.03	0.03	0.04	524	170	44.1	38.5	49.6	488

	Squamous cell carcinoma with variants middle ear	0.02	0.02	0.03	377	122	37.6	31.8	44.4	370
	Adenocarcinoma with variants of middle ear	0.00	0.00	0.00	50	16	83.8	70.5	99.5	50
Digestive rare cancers		21.94	21.86	22.01	343,635	112,351	15.3	15.2	15.5	321,375
	EPITHELIAL TUMOURS OF OESOPHAGUS	7.81	7.77	7.85	122,344	40,068	11.98	11.8	12.2	119,522
	Squamous cell carcinoma with variants of oesophagus	3.36	3.33	3.39	52,597	17,036	11.7	11.3	12.0	53,225
	Adenocarcinoma with variants of oesophagus	3.26	3.24	3.29	51,138	16,564	13.9	13.5	14.2	51,250
	Salivary gland type tumours of oesophagus	0.00	0.00	0.01	63	20	13.7	6.4	29.0	64
	Undifferentiated carcinoma of oesophagus	0.04	0.04	0.05	695	225	6.8	4.9	9.4	712
	RARE EPITHELIAL TUMOURS OF STOMACH	0.33	0.32	0.34	5,146	1,886	15.9	14.7	17.1	5,157
	Squamous cell carcinoma with variants of stomach	0.12	0.11	0.12	1,807	585	17.5	15.6	19.7	1,800
	Salivary gland-type tumours of stomach	0.00	0.00	0.00	39	13	25.1	12.7	49.9	40
	Undifferentiated carcinoma of stomach	0.21	0.20	0.22	3,300	1,069	14.9	13.5	16.4	3,317
	EPITHELIAL TUMOURS OF SMALL INTESTINE	0.77	0.76	0.79	12,132	3,930	27.3	26.3	28.3	11,544
	Adenocarcinoma with variants of small intestine	0.59	0.58	0.60	9,219	2,986	27.9	26.8	29.0	9,193
	Squamous cell carcinoma with variants of small intestine	0.01	0.01	0.01	133	43	34.8	26.8	45.3	133
	RARE EPITHELIAL TUMOUR OF COLON	0.13	0.13	0.14	2,074	737	54.8	52.0	57.7	2,075
	Squamous cell carcinoma with variants of colon	0.03	0.02	0.03	400	130	37.1	31.8	43.4	395
	Fibromixoma and low grade mucinous adenocarcinoma of the appendix	0.11	0.10	0.11	1,674	542	58.8	55.7	62.1	1,680
	RARE EPITHELIAL TUMOURS OF RECTUM	0.11	0.11	0.12	1,764	635	47.2	44.4	50.2	1,777
	Squamous cell carcinoma with variants of rectum	0.11	0.11	0.12	1,764	571	47.2	44.4	50.2	1,777
	EPITHELIAL TUMOURS OF ANAL CANAL	1.16	1.14	1.18	18,155	5,880	56.5	55.5	57.4	18,020
	Squamous cell carcinoma with variants of anal canal	0.81	0.80	0.82	12,691	4,111	63.0	61.9	64.1	12,847
	Adenocarcinoma with variants of anal canal	0.25	0.25	0.26	3,970	1,286	41.9	39.9	43.9	3,945
	Paget s disease of anal canal	0.00	0.00	0.00	21	7	62.9	38.0	104.0	21
	RARE EPITHELIAL TUMOURS OF PANCREAS	0.07	0.07	0.08	1,159	414	20.2	17.4	23.3	1,116
	Squamous cell carcinoma with variants of pancreas	0.02	0.02	0.03	361	117	5.9	3.6	9.6	347
	Acinar cell carcinoma of pancreas	0.03	0.03	0.03	449	145	19.0	14.8	24.3	427
	Mucinous cystadenocarcinoma of pancreas	0.01	0.01	0.01	109	35	35.9	26.3	49.0	106
	Intraductal papillary mucinous carcinoma invasive of pancreas	0.01	0.01	0.01	173	56	31.8	23.6	42.9	171
	Solid pseudopapillary carcinoma of pancreas	0.00	0.00	0.00	44	14	67.7	52.8	86.8	42
	Serous cystadenocarcinoma of pancreas	0.00	0.00	0.00	4	1	NE	NE	NE	4
	Carcinoma with osteoclast-like giant cells of pancreas	0.00	0.00	0.00	19	6	NE	NE	NE	19
	EPITHELIAL TUMOURS OF LIVER AND INTRAEPATIC BILE TRACT (IBT)	7.10	7.06	7.14	111,271	36,261	10.1	9.9	10.3	98,765
	Hepatocellular carcinoma of Liver and IBT	3.22	3.19	3.25	50,461	16,344	14.0	13.7	14.4	46,896

	Hepatocellular carcinoma, fibrolamellar of liver and IBT	0.02	0.02	0.03	387	125	28.1	23.3	33.8	390
	Cholangiocarcinoma of IBT	0.97	0.95	0.99	15,201	4,924	6.0	5.6	6.6	13,845
	Adenocarcinoma with variants of liver and IBT	0.41	0.40	0.42	6,457	2,091	6.6	5.9	7.4	6,311
	Undifferentiated carcinoma of liver and IBT	0.02	0.01	0.02	240	78	2.7	1.2	6.4	219
	Squamous cell carcinoma with variants of liver and IBT	0.01	0.01	0.01	147	48	14.6	9.1	23.4	143
	Bile duct cystadenocarcinoma of IBT	0.00	0.00	0.00	38	12	23.6	11.5	48.5	34
	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	4.44	4.41	4.48	69,590	22,540	13.6	13.2	13.9	63,889
	Adenocarcinoma with variants of gallbladder	1.35	1.33	1.36	21,085	6,830	14.5	14.0	15.1	20,338
	Adenocarcinoma with variants of EBT	1.44	1.42	1.46	22,510	7,291	19.2	18.6	19.8	22,234
	Squamous cell carcinoma of gallbladder and EBT	0.03	0.03	0.03	496	161	8.8	6.3	12.3	476
Thoracic rare cancers		6.80	6.76	6.84	106,573	37,277	13.4	13.1	13.6	104,670
	EPITHELIAL TUMOUR OF TRACHEA	0.11	0.11	0.12	1,771	574	18.0	16.0	20.3	1,697
	Squamous cell carcinoma with variants of trachea	0.06	0.06	0.07	1,017	329	12.2	10.0	14.9	1,008
	Adenocarcinoma with variants of trachea	0.01	0.01	0.01	164	53	15.7	10.3	24.0	158
	Salivary gland type tumours of trachea	0.01	0.01	0.01	175	57	70.1	62.0	79.2	174
	RARE EPITHELIAL TUMOUR OF LUNG	4.37	4.34	4.40	68,452	24,930	14.9	14.6	15.2	67,936
	Adenosquamous carcinoma of lung	0.29	0.29	0.30	4,607	1,492	21.9	20.5	23.4	4,566
	Large cell carcinoma of lung	3.81	3.78	3.84	59,714	19,342	13.9	13.5	14.2	59,332
	Salivary gland type tumours of lung	0.06	0.05	0.06	879	285	40.4	36.8	44.4	866
	Sarcomatoid carcinoma of lung	0.21	0.20	0.22	3,255	1,054	17.5	16.0	19.2	3,183
	EPITHELIAL TUMOURS OF THYMUS	0.18	0.17	0.19	2,795	905	64.3	62.1	66.6	2,729
	Malignant thymoma	0.14	0.14	0.15	2,268	735	69.3	67.0	71.8	2,248
	Squamous cell carcinoma of thymus	0.01	0.01	0.01	114	37	40.4	30.4	53.7	112
	Undifferentiated carcinoma of thymus	0.00	0.00	0.00	36	12	13.3	5.1	34.8	36
	Lymphoepithelial carcinoma of thymus	0.00	0.00	0.00	12	4	55.0	29.2	103.6	11
	Adenocarcinoma with variants of thymus	0.00	0.00	0.00	45	15	37.3	21.7	64.1	44
	MALIGNANT MESOTHELIOMA	2.14	2.12	2.16	33,552	10,868	5.3	4.9	5.6	32,330
	Mesothelioma of pleura and pericardium	1.83	1.81	1.85	28,676	9,288	4.6	4.2	4.9	27,893
	Mesothelioma of peritoneum and tunica vaginalis	0.13	0.13	0.14	2,065	669	13.2	11.5	15.1	1,965
Female genital rare cancers		22.73	22.66	22.81	356,151	113,796	57.7	57.5	57.9	347,015
	RARE EPITHELIAL TUMOURS OF BREAST	4.12	4.09	4.16	64,605	22,980	91.4	91.0	91.8	64,368
	Mammary Paget’s disease of breast	0.41	0.40	0.42	6,488	2,101	85.9	84.6	87.3	6,508

	Special types of adenocarcinoma of breast	3.06	3.04	3.09	48,012	15,551	95.2	94.8	95.6	47,974
	Metaplastic carcinoma of breast	0.10	0.10	0.11	1,576	510	65.0	61.9	68.3	1,583
	Salivary gland type tumours of breast	0.06	0.05	0.06	868	281	90.9	87.6	94.2	870
	Epithelial tumour of male breast	0.52	0.51	0.53	8,098	5,376	77.0	75.5	78.5	7,882
	RARE EPITHELIAL TUMOURS OF CORPUS UTERI	0.70	0.69	0.72	11,038	3,932	44.3	43.2	45.5	11,013
	Squamous cell carcinoma with variants of corpus uteri	0.06	0.06	0.07	1,003	325	58.2	54.6	62.1	989
	Adenoid cystic carcinoma of corpus uteri	0.00	0.00	0.00	5	2	64.1	31.3	131.1	5
	Clear cell adenocarcinoma, NOS of corpus uteri	0.16	0.16	0.17	2,527	819	58.6	56.2	61.2	2,532
	Serous (papillary) carcinoma of corpus uteri	0.08	0.07	0.08	1,227	397	40.0	36.5	43.9	1,225
	Mullerian mixed tumour of corpus uteri	0.40	0.39	0.41	6,276	2,033	36.9	35.5	38.4	6,263
	EPITHELIAL TUMOURS OF CERVIX UTERI	6.28	6.24	6.32	98,321	28,898	65.4	65.1	65.8	96,821
	Squamous cell carcinoma with variants of cervix uteri	4.73	4.70	4.76	74,105	24,003	66.8	66.5	67.2	73,810
	Adenocarcinoma with variants of cervix uteri	0.91	0.89	0.92	14,252	4,616	67.4	66.5	68.3	14,221
	Undifferentiated carcinoma of cervix uteri	0.03	0.03	0.03	480	155	35.3	30.9	40.4	478
	Mullerian mixed tumour of cervix uteri	0.02	0.01	0.02	257	83	34.3	28.1	41.7	256
	EPITHELIAL TUMOUR OF OVARY AND FALLOPPIAN TUBE	9.38	9.33	9.43	146,908	45,382	37.5	37.2	37.8	141,240
	Adenocarcinoma with variants of ovary	5.95	5.92	5.99	93,263	30,208	38.7	38.3	39.1	92,814
	Mucinous adenocarcinoma of ovary	0.77	0.76	0.78	12,066	3,908	59.9	58.9	60.9	12,010
	Clear cell adenocarcinoma of ovary	0.30	0.29	0.31	4,753	1,540	55.5	53.8	57.2	4,761
	Primary peritoneal serous/papillary carcinoma of ovary	0.08	0.08	0.09	1,280	415	21.9	19.1	25.2	1,280
	Mullerian mixed tumour of ovary	0.14	0.14	0.15	2,255	730	21.4	19.5	23.6	2,242
	Adenocarcinoma with variant of falloppian tube	0.17	0.16	0.18	2,683	869	59.1	56.8	61.6	2,672
	NON EPITHELIAL TUMOURS OF OVARY	0.25	0.25	0.26	3,977	1,288	82.0	80.6	83.5	3,970
	Sex cord tumours of ovary	0.13	0.12	0.13	2,006	650	78.8	76.5	81.1	1,998
	Malignant/Immature teratomas of ovary	0.05	0.05	0.06	833	270	83.4	80.6	86.3	829
	Germ cell tumour of ovary	0.07	0.07	0.08	1,138	369	86.6	84.4	88.8	1,143
	EPITHELIAL TUMOURS OF VULVA AND VAGINA	1.97	1.95	2.00	30,938	11,215	58.1	57.3	58.8	30,238
	Squamous cell carcinoma with variants of vulva and vagina	1.69	1.67	1.71	26,422	8,558	59.8	59.0	60.7	26,277
	Adenocarcinoma with variants of vulva and vagina	0.07	0.07	0.08	1,120	363	45.8	42.3	49.6	1,112
	Paget s disease of vulva and vagina	0.05	0.04	0.05	746	242	88.0	83.7	92.6	744
	Undifferentiated carcinoma of vulva and vagina	0.01	0.00	0.01	85	28	25.6	15.8	41.6	85
	TROPHOBLASTIC TUMOUR OF PLACENTA	0.02	0.02	0.03	363	100	89.3	85.3	92.2	361
	Choriocarcinoma of placenta	0.02	0.02	0.02	352	114	89.8	86.5	93.3	350
Male genital and urogenital rare cancers		7.09	7.05	7.14	111,128	38,138	73.64	73.3	74.0	109,102

	RARE EPITHELIAL TUMOURS OF PROSTATE	0.60	0.59	0.61	9,437	3,563	75.4	74.0	76.9	9,291
	Squamous cell carcinoma with variants of prostate	0.02	0.02	0.02	291	94	41.1	34.1	49.5	287
	Infiltrating duct carcinoma of prostate	0.51	0.50	0.53	8,064	2,612	78.7	77.2	80.3	7,945
	Transitional cell carcinoma of prostate	0.06	0.06	0.07	960	311	57.7	53.4	62.4	941
	Salivary gland type tumours of prostate	0.01	0.01	0.01	122	40	78.5	64.4	95.7	118
	TESTICULAR AND PARATESTICULAR CANCERS	3.29	3.27	3.32	51,605	16,061	94.9	94.7	95.2	51,011
	Paratesticular adenocarcinoma with variants	0.00	0.00	0.00	22	7	82.5	65.3	104.1	22
	Non seminomatous testicular cancer	1.27	1.25	1.28	19,835	6,425	92.9	92.5	93.3	19,714
	Seminomatous testicular cancer	1.82	1.80	1.84	28,516	9,236	97.5	97.3	97.8	28,326
	Spermatocytic seminoma	0.03	0.03	0.03	502	163	95.3	91.8	99.0	502
	Teratoma with malignant transformation	0.00	0.00	0.00	20	6	91.4	78.6	106.2	20
	Testicular sex cord cancer	0.02	0.02	0.02	340	110	82.3	77.3	87.6	337
	EPITHELIAL TUMOURS OF PENIS	0.66	0.65	0.67	10,368	3,887	67.5	66.2	68.9	10,210
	Squamous cell carcinoma with variants of penis	0.62	0.60	0.63	9,646	3,124	68.9	67.5	70.2	9,621
	Adenocarcinoma with variants of penis	0.01	0.00	0.01	88	29	49.0	36.2	66.4	86
	RARE EPITELIAL TUMOURS OF KIDNEY	0.05	0.04	0.05	723	261	18.8	15.8	22.4	704
	Squamous cell carcinoma spindle cell type of kidney	0.01	0.01	0.01	190	62	22.0	16.0	30.2	190
	Squamous cell carcinoma with variants of kidney	0.03	0.03	0.04	533	173	17.7	14.4	21.7	514
	EPITHELIAL TUMOURS OF PELVIS AND URETER	1.58	1.57	1.60	24,826	9,187	48.8	48.0	49.7	24,017
	Transitional cell carcinoma of pelvis and ureter	1.41	1.39	1.43	22,099	7,158	51.3	50.4	52.2	21,607
	Squamous cell carcinoma with variants of pelvis and ureter	0.02	0.02	0.03	372	121	15.0	11.2	20.2	366
	Adenocarcinoma with variants of pelvis and ureter	0.02	0.02	0.02	326	106	43.0	36.7	50.5	320
	EPITHELIAL TUMOURS OF URETHRA	0.13	0.13	0.14	2,077	784	44.5	41.6	47.5	2,050
	Transitional cell carcinoma of urethra	0.09	0.08	0.09	1,390	450	42.9	39.5	46.7	1,387
	Squamous cell carcinoma with variants of urethra	0.02	0.02	0.02	329	107	51.1	44.6	58.5	329
	Adenocarcinoma with variants of urethra	0.01	0.01	0.01	190	62	52.0	43.2	62.6	189
	RARE EPITHELIAL TUMOURS OF BLADDER	0.65	0.64	0.67	10,226	3,819	32.3	31.2	33.5	10,152
	Squamous cell carcinoma with variants of bladder	0.36	0.35	0.36	5,566	1,803	24.3	22.9	25.7	5,534
	Adenocarcinoma with variants of bladder	0.30	0.29	0.31	4,653	1,507	41.9	40.1	43.8	4,614
	Salivary gland type tumours of bladder	0.00	0.00	0.00	7	2	NE	NE	NE	7
	EXTRAGONADAL GERM CELL TUMOURS	0.12	0.11	0.12	1,862	576	69.6	67.3	71.8	1,851
	Non seminomatous germ cell tumours	0.06	0.05	0.06	915	296	62.5	59.2	66.0	909
	Seminomatous germ cell tumors	0.01	0.01	0.01	130	42	85.9	79.1	93.3	130
	Germ cell tumors of CNS	0.04	0.03	0.04	574	186	82.5	79.2	85.9	572
Neuroendocrine tumours		3.51	3.43	3.58	54,942	19,587	53.5	53.0	54.1	54,331

	NEUROENDOCRINE TUMOURS	3.51	3.48	3.54	54,942	19,587	53.5	53.0	54.1	54,331
	GEP, well diff not funct endocrine carcinoma of pancreas and digestive tract	1.01	1.00	1.03	15,852	5,134	72.0	71.1	73.0	15,656
	GEP, well diff funct endocrine carcinoma of pancreas and digestive tract	0.03	0.02	0.03	411	133	61.3	55.9	67.3	407
	GEP, poorly differentiated endocrine carcinoma	0.67	0.65	0.68	10,421	3,375	35.0	33.9	36.2	10,456
	GEP, mixed endocrine-exocrine carcinoma	0.01	0.01	0.01	147	48	25.9	18.2	37.0	141
	Endocrine carcinoma of thyroid gland	0.24	0.23	0.25	3,796	1,230	83.6	82.1	85.2	3,793
	Neuroendocrine carcinoma of skin	0.19	0.19	0.20	3,024	979	55.9	53.2	58.7	2,997
	Typical and atypical carcinoid of the lung	0.39	0.38	0.40	6,160	1,995	81.1	79.9	82.5	6,058
	Neuroendocrine carcinoma of other sites	0.90	0.89	0.92	14,120	4,573	23.9	23.0	24.8	13,958
	Pheochromocytoma, malignant	0.04	0.04	0.04	650	211	70.1	65.9	74.5	612
	Paraganglioma	0.02	0.02	0.02	347	112	56.3	50.6	62.6	342
Cancers of the endocrine organs		5.35	5.32	5.39	83,836	28,322	88.08	87.8	88.4	82,523
	CARCINOMAS OF PITUITARY GLAND	0.04	0.03	0.04	582	206	63.7	58.9	69.0	511
	Carcinoma of pituitary gland	0.04	0.03	0.04	582	206	63.7	58.9	69.0	511
	CARCINOMAS OF THYROID GLAND	5.07	5.03	5.10	79,418	26,768	90.5	90.2	90.8	78,533
	Carcinoma of thyroid gland	5.07	5.03	5.11	79,420	26,768	90.5	90.2	90.8	78,533
	CARCINOMAS OF PARATHYROID GLAND	0.03	0.02	0.03	410	143	80.8	75.8	86.2	395
	Carcinoma of parathyroid gland	0.03	0.02	0.03	410	143	80.8	75.8	86.2	395
	CARCINOMA OF ADRENAL GLAND	0.22	0.21	0.23	3,424	1,205	32.1	30.2	34.0	3,103
	Carcinoma of adrenal gland	0.22	0.21	0.23	3,424	1,205	32.1	30.2	34.0	3,103
Sarcomas		5.86	5.83	6.00	91,878	31,916	59.53	57.4	58.2	90,568
	SOFT TISSUE SARCOMA	4.71	4.68	4.74	73,795	25,851	56.7	56.3	57.1	72,696
	Soft tissue sarcoma of head and neck	0.26	0.25	0.27	4,087	1,324	59.8	57.7	61.8	4,062
	Soft tissue sarcoma of limbs	1.10	1.08	1.11	17,178	5,564	67.7	66.8	68.6	17,094
	Soft tissue sarcoma of superficial trunk	0.50	0.49	0.51	7,813	2,531	48.1	46.8	49.5	7,723
	Soft tissue sarcoma of mediastinum	0.03	0.03	0.03	465	151	23.4	19.3	28.3	457
	Soft tissue sarcoma of heart	0.01	0.01	0.02	216	70	14.4	9.8	21.0	203
	Soft tissue sarcoma of breast	0.18	0.18	0.19	2,865	928	74.5	72.5	76.5	2,864
	Soft tissue sarcoma of uterus	0.55	0.54	0.56	8,657	2,804	52.0	50.8	53.2	8,568
	Other soft tissue sarcomas of genitourinary tract	0.20	0.19	0.21	3,160	1,024	50.4	48.3	52.5	3,107
	Soft tissue sarcoma of viscera	0.38	0.37	0.39	6,004	1,945	42.1	40.6	43.6	5,915
	Soft tissue sarcoma of paratestis	0.03	0.03	0.04	510	165	87.2	82.2	92.4	510
	Soft tissue sarcoma of retroperitoneum and peritoneum	0.31	0.30	0.32	4,911	1,591	38.8	37.1	40.5	4,854

	Soft tissue sarcoma of pelvis	0.20	0.19	0.20	3,090	1,001	47.4	45.3	49.6	3,064
	Soft tissue sarcoma of skin	0.30	0.29	0.31	4,737	1,534	90.2	88.8	91.7	4,728
	Soft tissue sarcoma of paraorbit	0.01	0.01	0.01	117	38	63.3	52.9	75.7	115
	Soft tissue sarcoma of brain and other parts of nervous system	0.17	0.17	0.18	2,723	882	54.5	52.3	56.7	2,695
	Embryonal rhabdomyosarcoma of soft tissue	0.05	0.05	0.06	836	271	66.2	62.8	69.8	825
	Alveolar rhabdomyosarcoma of soft tissue	0.03	0.03	0.04	519	168	36.0	31.7	40.8	515
	Ewing's sarcoma of soft tissue	0.06	0.06	0.07	998	323	44.9	41.5	48.5	992
	BONE SARCOMA	0.85	0.84	0.87	13,376	4,382	58.6	57.6	59.6	13,216
	Osteogenic sarcoma	0.21	0.21	0.22	3,330	1,079	51.4	49.5	53.4	3,282
	Chondrogenic sarcomas	0.26	0.25	0.27	4,107	1,330	70.0	68.2	71.7	4,060
	Notochordal sarcomas, chordoma	0.07	0.07	0.08	1,145	371	62.5	58.2	67.2	755
	Vascular sarcomas	0.01	0.01	0.01	129	42	45.1	36.4	55.9	129
	Ewing's sarcoma	0.12	0.12	0.13	1,943	629	52.8	50.4	55.3	1,932
	Epithelial tumours, adamantinoma	0.01	0.01	0.02	213	69	87.2	81.0	93.9	210
	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0.02	0.02	0.02	304	98	46.2	40.1	53.1	302
	GASTROINTESTINAL STROMAL SARCOMA	0.30	0.29	0.31	4,706	1,683	72.3	70.4	74.1	4,781
	Gastrointestinal stromal sarcoma	0.30	0.29	0.31	4,706	1,524	72.3	70.4	74.1	4,781
Cancers of the central nervous system (CNS)		7.56	7.51	8.00	118,391	36,343	21.3	21.0	21.6	111,838
	TUMOURS OF CENTRAL NERVOUS SYSTEM (CNS)**	7.36	7.32	7.40	115,289	35,339	20.3	20.0	20.6	108,752
	Astrocytic tumours of CNS	4.99	4.95	5.02	78,118	25,303	15.0	14.8	15.3	77,195
	Oligodendroglial tumours of CNS	0.39	0.38	0.40	6,148	1,991	51.8	50.4	53.3	6,124
	Ependymal tumours of CNS	0.21	0.20	0.21	3,212	1,040	72.7	71.0	74.5	3,190
	Choroid plexus carcinoma of CNS	0.01	0.01	0.01	98	32	57.7	48.3	68.8	95
	Malignant meningiomas	0.16	0.16	0.17	2,564	830	61.1	58.8	63.4	2,509
	EMBRYONAL TUMORS OF CNS	0.20	0.19	0.21	3,102	1,005	56.1	54.2	58.1	3,092
	Embryonal tumors of CNS	0.20	0.19	0.21	3,102	1,005	56.1	54.2	58.1	3,092
Rare skin cancers and non-cutaneous melanoma		1.22	1.18	1.25	21,878	7,086	70.2	69.3	71.1	21,637
	MALIGNANT MELANOMA OF MUCOSA	0.15	0.14	0.15	2,279	738	20.3	18.2	22.6	2,277
	Malignant melanoma of mucosa	0.15	0.14	0.15	2,279	738	20.3	18.3	22.6	2,277
	MALIGNANT MELANOMA OF UVEA	0.70	0.69	0.72	11,022	3,570	71.0	69.8	72.2	10,872

	Malignant melanoma of uvea	0.70	0.69	0.72	11,022	3,570	71.0	69.8	72.2	10,872
	ADNEXAL CARCINOMA OF SKIN	0.30	0.29	0.31	4,684	1,517	86.1	83.9	88.0	4,661
	Adnexal carcinoma of skin	0.30	0.29	0.31	4,684	1,517	86.1	83.9	88.0	4,661
	KAPOSI'S SARCOMA	0.25	0.24	0.26	3,893	1,261	78.9	77.0	80.7	3,830
	Kaposi's sarcoma	0.25	0.24	0.26	3,893	1,261	78.9	77.1	80.8	3,830
Embrional tumours		0.34	0.33	0.35	5,363	1,822	78.6	77.4	79.8	5,239
	NEUROBLASTOMA AND GANGLIONEUROBLASTOMA	0.10	0.10	0.11	1,566	499	64.6	62.1	67.3	1,553
	Neuroblastoma e ganglioneuroblastoma	0.10	0.10	0.11	1,566	507	64.6	62.1	67.3	1,553
	NEPHROBLASTOMA	0.13	0.12	0.13	1,965	636	88.2	86.6	89.7	1,936
	Nephroblastoma	0.13	0.12	0.13	1,965	636	88.2	86.6	89.7	1,936
	RETINOBLASTOMA	0.05	0.05	0.06	860	279	96.5	95.1	97.9	801
	Retinoblastoma	0.05	0.05	0.06	860	279	96.5	95.1	97.9	801
	HEPATOBLASTOMA	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	Hepatoblastoma	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	PLEUROPULMONARY BLASTOMA	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	Pleuropulmonary blastoma	0.00	0.00	0.00	9	3	53.5	28.3	101.1	9
	PANCREATOBLASTOMA	0.00	0.00	0.00	9	3	53.5	28.3	101.1	9
	Pancreatoblastoma	0.00	0.00	0.00	39	13	34.3	20.7	56.9	35
	OLFACTORY NEUROBLASTOMA	0.00	0.00	0.00	39	13	34.3	20.7	56.9	35
	Olfactory neuroblastoma	0.03	0.03	0.03	498	161	64.0	59.2	69.2	489
	ODONTOGENIC MALIGNANT TUMOURS	0.03	0.03	0.03	498	161	64.0	59.2	69.2	489
	Odontogenic malignant tumours	0.00	0.00	0.01	69	22	61.6	49.0	77.5	69
Haematological rare malignancies		27.73	27.65	27.82	434,469	156,099	50.5	50.3	50.7	423,741
	RARE LYMPHOID DISEASES	18.09	18.02	18.16	283,399	100,343	55.8	55.5	56.0	279,794
	Hodgkin lymphoma, classical	2.46	2.44	2.49	38,588	12,499	81.4	80.9	81.8	38,389
	Hodgkin lymphoma nodular lymphocyte predominance	0.09	0.09	0.10	1,483	480	93.6	91.8	95.3	1,507
	Precursor B/T lymphoblastic leuk/lymphoma (and Burkitt leukemia/lymphoma)	1.46	1.44	1.47	22,795	7,383	58.1	57.4	58.8	22,496
	T cutaneous lymphoma (Sezary syn, Mycosis fung)	0.35	0.34	0.36	5,526	1,790	81.5	80.0	83.1	5,482
	Other T cell lymphomas and NK cell neoplasms	0.62	0.60	0.63	9,656	3,128	39.0	37.9	40.2	9,635
	Diffuse B lymphoma	4.32	4.29	4.35	67,645	21,910	53.4	52.9	53.9	67,907
	Follicular B lymphoma	2.19	2.17	2.22	34,346	11,125	77.0	76.4	77.6	34,545
	Hairy cell leukaemia	0.28	0.27	0.29	4,375	1,417	89.8	88.3	91.3	4,387
	Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	5.71	5.67	5.75	89,440	28,970	35.3	34.8	35.7	86,496

	Mantle cell lymphoma	0.56	0.55	0.57	8,748	2,834	44.0	42.6	45.4	8,797
	Prolymphocytic leukaemia, B cell	0.05	0.05	0.06	804	260	30.8	26.9	35.2	788
	ACUTE MYELOID LEUKEMIA AND RELATED PRECURSOR NEOPLASMS	3.81	3.77	3.84	59,608	21,557	19.2	18.8	19.6	56,709
	Acute promyelocytic leukemia (AML with t(15;17) with variants	0.12	0.11	0.13	1,876	608	63.2	60.8	65.7	1,880
	Acute myeloid leukemia	3.50	3.47	3.53	54,789	17,746	17.5	17.1	17.8	52,305
	MYELOPROLIFERATIVE NEOPLASMS	3.31	3.28	3.34	51,888	18,805	68.3	67.7	68.9	50,624
	Chronic myeloid leukemia	1.12	1.10	1.13	17,473	5,660	54.9	54.0	55.9	16,599
	Other myeloproliferative neoplasms	2.17	2.14	2.19	33,954	10,998	75.0	74.3	75.7	33,599
	Mast cell tumour	0.03	0.03	0.03	461	149	71.4	66.2	77.1	454
	MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	2.47	2.45	2.50	38,738	15,116	31.1	30.5	31.8	37,792
	Myelodysplastic syndrome with 5q syndrome	0.01	0.01	0.01	156	51	48.0	38.3	60.3	178
	Other myelodysplastic syndrome	2.14	2.12	2.16	33,542	10,864	32.2	31.5	32.9	32,576
	Chronic Myelomonocytic leukemia	0.29	0.28	0.30	4,542	1,471	21.3	19.8	23.0	4,575
	Atypical chronic myeloid leukemia BCR/ABL negative	0.02	0.01	0.02	239	77	28.2	21.7	36.5	248
	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	0.05	0.05	0.06	828	278	59.9	56.1	63.9	817
	Histiocytic malignancies	0.04	0.04	0.05	656	212	63.4	59.4	67.8	645
	Lymph node accessory cell tumors	0.01	0.01	0.01	172	56	45.6	37.1	56.0	172
All rare tumours	**ALL RARE TIER2 TUMOURS**	114.99	114.82	115.16	1,801,443	636,753	48.5	48.4	48.6	1,751,601

COMMON CANCERS

Digestive common tumours		91.80	91.65	91.95	1,438,094	490,051	41.4	41.3	45.8	1,365,575
	EPITHELIAL TUMOURS OF STOMACH	17.10	17.03	17.16	267,832	92,067	21.2	21.0	21.4	253,439
	Adenocarcinoma with variants of stomach	14.18	14.12	14.24	222,145	71,954	22.7	22.5	22.9	221,604
	EPITHELIAL TUMOUR OF COLON	43.88	43.77	43.98	687,386	234,319	54.2	54.0	54.4	664,118
	Adenocarcinoma with variants of colon	38.85	38.75	38.95	608,637	197,139	57.9	57.7	58.0	604,459
	EPITHELIAL TUMOURS OF RECTUM	17.98	17.92	18.05	281,697	95,187	53.8	53.6	54.1	276,024
	Adenocarcinoma with variants of rectum	16.45	16.39	16.52	257,723	83,477	55.8	55.6	56.1	258,469
	EPITHELIAL TUMOURS OF PANCREAS	12.84	12.79	12.90	201,179	68,478	4.1	4.0	4.2	182,579
	Adenocarcinoma with variants of pancreas	7.96	7.92	8.01	124,744	40,405	4.1	4.0	4.2	119,154
Thoracic common tumours		53.02	52.91	53.14	830,611	281,332	10.1	10.0	10.2	779,539

	EPITHELIAL TUMOUR OF LUNG	53.02	52.91	53.14	830,611	281,332	10.1	10.0	10.2	779,539
	Squamous cell carcinoma with variants of lung	12.31	12.25	12.36	192,771	62,439	5.9	13.7	14.1	121,904
	Adenocarcinoma with variants of lung	11.63	11.58	11.68	182,175	59,007	40.4	15.9	16.3	866
	Poorly differentiated endocrine carcinoma of lung	7.91	7.86	7.95	123,888	40,128	17.5	5.7	6.0	3,183
Female genital common tumours		74.17	74.03	74.30	1,161,864	394,087	82.20	82.10	82.30	1,131,902
	EPITHELIAL TUMOURS OF BREAST	63.52	63.40	63.65	995,119	318,878	82.4	82.3	82.5	971,037
	Invasive ductal carcinoma of breast	46.56	46.45	46.66	729,345	236,237	85.4	85.3	85.6	723,998
	Invasive lobular carcinoma of breast	7.75	7.71	7.80	121,455	39,340	86.2	85.9	86.5	120,973
	EPITHELIAL TUMOURS OF CORPUS UTERI	10.64	10.59	10.70	166,745	75,209	81.2	80.9	81.4	164,787
	Adenocarcinoma with variants of corpus uteri	9.93	9.88	9.98	155,550	50,383	83.0	82.7	83.2	154,968
Male genital and urogenital common tumours		85.27	85.13	85.42	1,335,876	462,665	75.90	75.80	76.00	1,277,743
	EPITHELIAL TUMOURS OF PROSTATE	55.06	54.95	55.18	862,576	301,113	84.0	83.8	84.1	842,467
	Adenocarcinoma with variants of prostate	48.86	48.75	48.97	765,405	247,917	88.1	88.0	88.3	762,360
	EPITELIAL TUMOURS OF KIDNEY	12.66	12.61	12.72	198,402	65,848	60.5	60.2	60.7	187,324
	Renal cell carcinoma with variants	10.08	10.03	10.13	157,886	51,140	68.5	68.2	68.8	153,460
	EPITHELIAL TUMOURS OF BLADDER	17.55	17.48	17.61	274,896	95,704	60.4	60.1	60.6	266,941
	Transitional cell carcinoma of bladder	15.68	15.62	15.74	245,681	79,577	62.7	62.4	63.0	243,620
Common skin tumours and non-cutaneous melanoma		69.08	68.95	69.21	1,082,244	350,542	95.6	95.5	95.7	1,048,046
	MALIGNANT SKIN MELANOMA	14.06	14.00	14.12	220,206	71,325	83.8	83.6	84.0	216,317
	Malignant skin melanoma	14.06	14.00	14.12	220,206	71,325	83.8	83.6	84.1	216,317
	EPITHELIAL TUMOURS OF SKIN	55.03	54.91	55.14	862,038	279,217	98.8	98.7	99	837,895
	Basal cell carcinoma of skin	40.75	40.65	40.85	638,347	206,763	101.6	101.5	101.8	634,953
	Squamous cell carcinoma with variants of skin	14.28	14.22	14.34	223,691	72,454	89.7	89.4	90.1	221,487
Haematological common malignancies		11.03	10.98	11.08	172,794	58,286	60.5	60.2	60.8	166,040
	LYMPHOID DISEASES	11.03	10.98	11.08	172,794	58,286	60.5	60.2	60.8	166,040
	Other non Hodgkin, Mature B cell lymphoma	6.37	6.33	6.41	99,729	32,303	68.3	67.8	68.7	97,389

All common tumours	**ALL COMMON**	384.37	384.07	384.78	6,021,483	2,036,963	63.4	63.3	63.4	5,633,710

Note: the first tier entities (capital letters) are not a sum of the second tiers (small letters) included because of the NOS entities

NE= not estimable

Table 2. Age standardized incidence (IR) in 1999-2002 and 2003-2007, and corresponding Annual Percent Changes (APC) between the two periods, of rare cancers lying outside the 3-standard-errors confidence bounds in Figure 1

Cancer entity	1999-2002 IR	2003-2007 IR	APC	99.8% Confidence interval	
				lower	upper
Gastrointestinal stromal sarcoma	0.098	0.258	24.1	12.0	36.2
GEP, Poorly differentiated endocrine carcinoma of pancreas and digestive system	0.361	0.618	12.7	7.7	17.8
Other T cell lymphomas and NK cell neoplasms	0.395	0.555	7.8	3.3	12.4
Diffuse B lymphoma	2.837	3.894	7.3	5.7	8.9
Other myeloproliferative neoplasms	1.530	2.092	7.2	5.0	9.4
Mantle cell lymphoma	0.367	0.477	6.0	1.6	10.4
Carcinomas of thyroid gland	3.470	4.353	5.2	3.7	6.6
Other myelodysplastic syndrome	1.395	1.738	5.0	3.0	7.1
Squamous cell carcinoma with variants of anal canal	0.595	0.728	4.6	1.2	8.0
Follicular B lymphoma	1.676	2.021	4.2	2.2	6.3
Cholangiocarcinoma of IBT	0.685	0.816	4.0	0.9	7.0
Neuroendocrine carcinoma of other sites	0.683	0.801	3.6	0.5	6.7
Adenocarcinoma with variants of oesophagus	2.725	3.153	3.3	1.8	4.8
Squamous cell carcinoma with variants of oropharynx	2.412	2.732	2.8	1.1	4.5
Adenocarcinoma with variants of EBT	0.969	1.088	2.6	0.1	5.1
Hepatocellular carcinoma of Liver and IBT	2.068	2.273	2.1	0.4	3.8
Squamous cell carcinoma with variants of cervix uteri	4.536	4.287	-1.2	-2.4	-0.1
Adenocarcinoma with variants of ovary	5.351	5.053	-1.3	-2.3	-0.2

Squamous cell carcinoma with variants of larynx	3.853	3.578	-1.6	-2.8	-0.4
Chronic myeloid leukemia	0.991	0.854	-3.2	-5.5	-0.9
Infiltrating duct carcinoma of prostate	0.412	0.343	-4.0	-7.4	-0.6
Squamous cell carcinoma with variants of lip	0.838	0.693	-4.1	-6.5	-1.8
Large cell carcinoma of lung	3.440	2.806	-4.4	-5.6	-3.2
Mucinous adenocarcinoma of ovary	0.813	0.657	-4.6	-7.2	-2.1
Adenocarcinoma with variants of bladder	0.265	0.213	-4.7	-8.9	-0.5
Undifferentiated carcinoma of stomach	0.189	0.123	-9.2	-13.9	-4.5

Table 3. Age standardized 5-year relative survival (RS) in 1999-2001 and 2005-2007, and corresponding difference between the two periods, of rare cancers lying outside the 3-standard-errors confidence bounds in Figure 2

Cancer entity	1999-2001 5-year RS	2005-2007 5-year RS	Difference	99.8% Confidence interval	
				lower	upper
Chronic myeloid leukemia	37.2	57.9	20.7	17.4	24.1
Infiltrating duct carcinoma of prostate	67.5	79.8	12.3	6.4	18.2
Soft tissue sarcoma of viscera	34.7	43.7	9.0	3.6	14.4
Kaposi's sarcoma	75.4	84.2	8.8	1.4	16.2
Diffuse B lymphoma	46.9	55.2	8.4	6.5	10.2
Follicular B lymphoma	69.5	77.9	8.4	5.9	10.8
GEP, Poorly differentiated endocrine carcinoma of pancreas and digestive system	25.3	32.7	7.5	2.7	12.2
Squamous cell carcinoma with variants of oropharynx	37.5	44.5	7.1	5.0	9.2
Soft tissue sarcoma of superficial trunk	43.9	50.4	6.5	1.4	11.6
Precursor B/T lymphoblastic leukemia/lymphoma (and Burkitt leukemia/lymphoma)	54.3	60.8	6.4	3.8	9.1
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	29.8	35.0	5.2	3.8	6.7
Carcinomas of thyroid gland	85.6	90.6	5.0	3.8	6.3
Adenocarcinoma with variants of cervix uteri	63.8	68.8	5.0	1.7	8.3
GEP, Well differentiated not functing endocrine carcinoma of pancreas and digestive system	67.7	72.6	4.9	1.5	8.4

Soft tissue sarcoma of limbs	63.9	68.4	4.4	1.0	7.9
Adenocarcinoma with variants of oesophagus	9.9	13.8	3.9	2.6	5.1
Squamous cell carcinoma with variants of oral cavity	46.1	49.7	3.7	1.7	5.6
Squamous cell carcinoma with variants of hypopharynx	22.2	25.6	3.4	0.5	6.3
Other myeloproliferative neoplasms	70.8	74.0	3.2	0.6	5.9
Squamous cell carcinoma with variants of cervix uteri	65.1	68.1	3.0	1.6	4.5
Large cell carcinoma of lung	10.9	13.6	2.7	1.6	3.9
Adenocarcinoma with variants of EBT	16.2	18.7	2.6	0.2	5.0
Squamous cell carcinoma with variants of oesophagus	9.5	12.0	2.5	1.3	3.7
Hepatocellular carcinoma of Liver and IBT	11.0	13.0	2.0	0.5	3.5
Other myelodysplastic syndrome	33.8	30.2	-3.5	-6.3	-0.8

Table 4. Annual number of cases, number of hospitals providing 75% of treatments (H75), mean annual number of treatments (treat) provided by H75 hospitals, by country and cancer group

	Country, population (millions)																			
Group of cancer	**Belgium (10.5)**			**Bulgaria (7.7)**			**Finland (5.3)**			**Ireland (4.2)**			**Netherlands (16.3)**			**Slovenia (2.0)**			**Navarra (0.6)**		
	cases	**H75**	**treat**	**cases**	**H75**	**treat**	**cases**	**H75**	**treat**	**cases**	**H75**	**treat**	**cases**	**H75**	**treat**	**cases**	**H75**	**treat**	**cases**	**H75**	**treat**
Haed & Neck	2,098	29	105.6	1,180	10	145.1	439	6	82.2	368	7	63.0	2,439	12	201.4	395	2	266.1	125	2	76.6
Epithelial Ovary	760	50	19.5	627	16	52.3	370	10	44.5	261	15	21.0	1,118	47	30.2	158	3	82.0	38	1	45.5
Oesophagus	689	31	29.3	77	14	5.2	163	8	21.6	289	9	37.1	1,422	31	42.0	49	2	32.9	24	2	15.7
Central Nervous System	623	20	48.4	412	13	41.7	57	4	19.1	229	3	106.3	912	14	84.0	97	2	78.7	47	2	32.0
Soft Tissue Sarcoma	500	35	16.6	372	21	18.4	165	7	25.6	157	17	10.6	802	33	26.4	81	2	47.4	32	2	17.4
Thyroid	576	34	14.2	220	12	20.4	286	12	22.8	98	11	9.6	418	31	17.1	109	1	260.3	43	2	36.8
Testis	244	40	8.4	180	19	12.4	101	9	14.3	144	12	15.6	609	42	18.4	93	3	48.8	10	3	4.4
Biliary Tract	214	44	4.9	183	23	6.5	147	13	11.3	122	14	7.7	582	38	12.2	47	3	13.2	43	2	19.7
GEP	287	46	5.6	30	21	1.3	148	13	9.3	61	20	2.7	355	44	6.9	22	3	6.8	10	3	2.9
Liver	250	22	11.0	107	12	7.6	165	11	12.8	68	12	4.6	236	36	5.2	29	2	14.4	49	3	14.5
Urinary Tract	292	48	6.7	67	17	4.1	48	12	3.9	24	10	2.3	419	46	7.7	30	3	8.9	19	3	8.2
Mesothelioma	184	25	8.7	34	10	3.7	64	9	6.8	25	11	2.0	481	43	9.8	21	1	22.3	9	2	4.6

Vagina	172	35	5.8	120	9	14.0	70	5	14.8	40	9	4.7	296	14	21.8	42	2	21.9	8	2	4.7
Bone Sarcoma	81	10	10.2	55	13	4.6	28	3	9.6	30	7	5.2	195	5	43.3	15	2	10.4	3	2	2.4
Anal Canal	95	27	5.3	39	12	4.1	24	7	4.6	30	9	4.4	135	22	7.2	15	1	23.6	4	2	3.6
Melanoma of uvea	43	2	21.9	17	7	2.7	6	1	5.5	29	4	5.7	156	2	80.2	13	1	11.9	3	3	0.8
Penis	63	43	1.4	39	17	2.4	21	10	2.1	20	15	1.2	109	26	3.7	9	4	2.0	4	3	1.2
Small Intestine	62	37	1.9	15	13	1.1	26	13	2.1	27	20	1.3	120	38	2.6	5	4	1.3	2	2	1.0
Neuroendocrine carcinoma of skin	46	32	1.9	1	3	0.4	0			15	18	0.8	77	37	2.3	4	4	1.1	0		
Non epithelial Ovary	20	19	1.3	43	17	3.2	8	9	1.1	8	15	0.6	32	24	1.4	4	3	1.7	1	3	0.3
Endocrine carcinoma of thyroid	31	22	1.4	10	9	1.2	8	8	1.2	5	10	0.5	32	13	2.7	5	1	10.3	1	1	1.7
Thymus	22	20	1.4	7	8	1.3	4	5	1.1	5	5	1.3	36	15	2.8	3	2	2.1	2	2	1.3
Nephroblastoma	18	4	7.4	6	3	2.8	8	3	4.7	7	1	13.4	30	4	16.9	3	1	4.8	0	1	0.3
Melanoma of mucosa	14	24	0.8	2	5	0.8	10	7	1.7	6	11	0.6	34	13	3.0	4	3	1.5	1	2	0.3
Adrenal cortex	13	14	1.1	13	10	1.3	6	7	0.9	5	11	0.4	25	15	1.5	3	2	1.4	1	2	0.4
Embryonal CNS	21	9	4.2	14	9	2.5	6	3	3.1	9	3	6.3	0				2	4.2	2	1	5.2
Neuroblastoma	15	4	5.7	8	5	1.7	1	1	2.1	7	2	5.4	12	4	6.2	1	2	1.3	1	1	1.8
Retinoblastoma	10	1	14.0	3	5	0.5	3	2	1.5	3	2	1.8	22	1	30.7	1	1	1.1	1	2	0.5
Trachea	10	18	0.9	5	4	1.1	4	5	0.9	2	4	0.4	11	11	1.1	3	1	3.8	1	1	0.5

Burden, time trends and centralized treatment of rare tumors: a European perspective.

The RARECAREnet population-based Project

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Summary

Background

Rare cancers here defined as those with an annual incidence rate less than 6/100,000 in Europe, pose challenges for diagnosis, treatments, and clinical decision-making. Information on rare cancers is scant. We updated the estimates of the burden of rare cancers in Europe, their time trends in incidence and survival, and provide information on centralization of treatments in seven European countries.

Methods

We analysed data on more than two million rare cancer diagnoses, provided by 83 cancer registries, to estimate European incidence and survival in 2000-2007 and the corresponding time trends during 1995-2007. Incidence rates were calculated as the number of new cases divided by the corresponding total person years in the population. Five-year relative survival (RS) was calculated by the Ederer-2 method. Seven registries (Belgium, Bulgaria, Finland, Ireland, Netherlands, Slovenia, and the Navarra region in Spain) provided additional data on hospitals of treatment for about 220,000 cases diagnosed in 2000-2007. Hospital volume was calculated as the number of treatments provided by each hospital rare cancer group sharing the same referral pattern.

Findings

Rare cancers accounted for 24% of all cancers diagnosed in EU28 during 2000-2007. The overall incidence rose yearly by 2.3%. RS increased (overall 5.7%), from 1999-2001 to 2007-2009, and for the majority of rare cancers, with the largest increases for hematological tumors and sarcomas. The level of centralization of rare cancer treatment varied widely between cancers and between countries. The Netherlands and Slovenia had the highest treatment volumes.

Interpretation

The study profits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk

factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments and better case management. There is ample room for improving the centralization of treatment in these seven European countries.

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Introduction

The RARECARE project defined rare cancers as those with an annual incidence rate less than 6/100,000 in Europe (EU), and showed that about one in five were rare types and slightly more than four million rare cancers were prevalent in the EU population [1]. Because of their low numbers, the almost 200 rare cancers listed by RARECARE pose challenges for diagnosis, treatments, and clinical decision-making. Clinical trials are rare too, and it is hard to build up new knowledge and expertise.

There is a broad consensus that the diagnostic pathologic confirmation and primary treatment of rare cancers, in particular, should be centralized in reference centers and/or in collaborative networks, with multidisciplinary approaches [2] and very specific expertise. In addition, clinical and translational research calls for a high level of centralization and international collaboration. To what extent appropriate policies for rare cancer patients are implemented at the country level has seldom been studied. As a consequence, information for policy makers and stakeholders is scarce for many of these tumors.

The project Information Network on Rare Cancers (RARECAREnet) is designed to update epidemiological information on rare cancers in the EU [3], to provide indicators at the country level, time trends, and to study to what extent treatment is centralized in Europe.

This paper provides up-to-date incidence and survival estimates based on data collected from 94 population-based cancer registries (CRs), for 198 rare cancers diagnosed in 2000-2007 and for

12 major families of rare cancers. It also presents data on the levels of centralization for rare cancers in selected European countries.

Material and Methods

Patients

The data were extracted from two databases. The first, the descriptive analysis database, is a subset of the EUROCARE-5 database [4]. It includes incidence and follow-up data provided by European population-based CRs regarding cancer patients diagnosed in the period~~-~~ Jan 1,1978~~,~~ to Dec 31, 2007.~~1978-2007~~. Vital status was updated to ~~-~~Dec 31, 2008.~~the end of 2008~~. From the 117 CRs participating in EUROCARE-5, we excluded specialized pediatric CRs, the Swedish and Turin CRs, because they did not participate in the RARECAREnet study, and the Danish CR, because it provided none of the details on morphology needed to define rare cancers. Details of the RARECAREnet database can be found in the report on the project website [5]. For the analysis of incidence we excluded 11 CRs specialized in specific anatomical sites to avoid incomplete coverage of some cancer entities affecting multiple sites such as neuroendocrine tumors. A total of 1,984,147 rare cancer diagnoses were considered for incidence estimates in 2000-2007, collected by 83 CRs from 1,566 million person-years of observation. Data for incidence trends came from 42 CRs covering the period 1995-2007, and included 2,268,602 cases, and 1,900 million person-years of observation. Survival estimates in 2000-2007 for all the rare cancers were based on a total of 1,994,346 diagnoses, observed by 94 CRs. Case identified only with death certificate (DCO) or casually discovered at autopsy were excluded from the analysis because they do not report time of survival. Cases lost to follow-up were considered as censored at the date of last contact. Multiple primaries in a same patient were included. Death certificate only (DCO) and autopsy cases were excluded but data included multiple primaries in a single patient. Finally, survival trend analysis was based on 1,649,309 rare cancer diagnoses from 45 CRs providing uninterrupted data from at least~~-~~Jan 1, 1995 to Dec 31, 2007.

~~1995 to 2007~~.

The second database was used for the study of hospitals of treatment and hospital volume. It comes from seven European CRs: the national CRs of Belgium, Bulgaria, Finland, Ireland, Netherlands, Slovenia, and the regional CR of Navarra (Spain). This last, although regional, was added in consideration of the regional organization of the Spanish health care system. These CRs were selected to reflect the variability of incidence and survival in Europe [1,5], and because they could provide detailed data for all 198 rare cancers. Variables included: sex, dates of birth and diagnosis, ~~from the International Classification of Disease for Oncology version 3 ICDO-3~~ topography and morphology codes from the International Classification of Disease for Oncology version 3 (ICDO-3), grading, pathological and clinical TNM, simplified stage (localized, regional extension, metastatic), treatment (surgery, radiotherapy, systemic, other or none), vital status, date of closure of follow-up or death, hospital of diagnosis and hospital of treatment. DCO and autopsy cases (1.3% overall, with a maximum of 8.6% in Bulgaria) were not included. The hospital of diagnosis was defined as the hospital where the pathology examination was done or requested. The hospital of treatment(s) was defined as the hospital where a specific treatment (e.g. surgery) or the first course of systemic therapy (e.g. chemotherapy) was given. Up to five different types of treatment within one year from the date of diagnosis were considered as a primary treatment. Vital status was further updated, with respect to the descriptive analysis database, to Dec 31, 2012.~~to the end of 2012.~~

We received data on about 348,000 rare cancers diagnosed in the period 2000-2007. However, national data from Belgium were limited to the period of diagnosis 2004-2007, and those from Navarra to 2000-2005. Cases diagnosed in Bulgaria and the Netherlands during 2000-2004 were removed on account of incomplete national coverage of hospital information. A total of 223,081 rare cancer cases were included in the hospital volume study database. Unspecific morphologies (8000, 8001, 8010, 8800, 9800, 9590) were found in 2.1% of cases, with the highest proportion (4.1%) in Finland. Seventeen per cent of cases (37,959/223,081) was removed, because for them the information of hospital was missing.

Methods

Rationale of the definition of rare cancer entities and their classification in terms of ICD-O codes are reported elsewhere [1,2,5]. Classification was structured in way to avoid any overlapping among rare entities. For example, GEP NET and GIST tumours were under the families of NET and sarcomas, and not also in digestive rare cancers.

Incidence rates were estimated as the number of new cases arising in 2000-2007 divided by the corresponding total person years (male + female) in the general population. The European standard population was used for direct age standardization. New cases in 2013 in EU28 were

calculated by multiplying age- and sex-specific incidence rates in 2000-2007 by the corresponding European population classified in five-year age classes on 1 January 2013.

Incidence variation over time was estimated restricting the analysis to 1,480,424 cases diagnosed in the two sub-periods 1999-2002 and 2003-07, and was presented in a funnel plot where each dot represents a single rare cancer, the y-axis displays the estimated difference in terms of annual percent change (APC) of age-adjusted incidence, and the x-axis the corresponding precision in terms of the inverse of its standard error. APC was calculated as the ratio between incidence rates for the two sub-periods elevated to 1/4.5, the inverse of their mean time distance. Three-standard-deviation confidence intervals for estimated zero changes [6] are represented by two symmetrical lines progressively approaching the x-axis with increasing x values. Dots lying above or below the area between them correspond respectively to tumors with 99.8% significantly higher or lower incidence rates.

Five-year relative survival (RS) was estimated as the ratio of observed to expected survival in the general population, matched by age, sex, calendar year, and geographical area, and calculated by the Ederer-2 method [7]. RS time trends were estimated by the period approach considering three follow-up periods: 1999-2001 (cohorts diagnosed- in Jan 1,1995 to Dec 31, 2001~~in 1995-2001~~), 2002-04 (cohorts diagnosed in- Jan 1,1998 to Dec 31, 2004~~1998-2004~~), and 2005-07 (cohorts diagnosed in- Jan 1, 2001 to Dec 31, 2007~~2001-07~~). RS changes were presented as a funnel plot, similarly to incidence changes, but using the difference between five-year RS in the last and first of these periods on the y-axis.

The volume (number) of treatments provided by each hospital was calculated for major cancer groups, defined by aggregating all the solid rare cancers into 38 groups sharing the same referral pattern (see Figure 3). For example, all the 17 head and neck tumors, identified [1] as clinically distinct rare entities, ~~head and neck tumors~~ are usually referred to head and neck specialized services, and were considered as a single group. Hematological rare tumors, not always requiring hospitalization, were not considered in the volume analysis. Hospital volume for each of the 38 groups was then

computed as the annual number of *any* treatment delivered by the hospital, for all the cancers in that group. Repeated admissions to the same hospital for the same cancer and the same treatment type (i.e. surgery, radiotherapy or systemic therapy) were considered as a single admission and counted as one treatment in the analyses. Instead, repeated admissions for several treatment types (such as radiotherapy and subsequent surgery) given to a patient in the same hospital were all counted as treatments. Untreated patients were assigned to the hospital of diagnosis. The total number of treatments provided by each hospital for a given group of rare cancers was then divided by the number of years of observation to provide its mean annual hospital volume.

Finally, for each patient we calculated the mean annual volume of the hospital(s) where they were treated, so obtaining a patient-specific measure with a much less skewed distribution with respect to the hospital-specific volume. Averaging this measure over all the patients diagnosed with a given group of rare cancers in a certain country gives a cancer- and country-specific measure of the level of expertise that patients can expect for the treatment of their tumor. We called it the *mean admission volume* (MAV) indicator.

Role of the funding source

The funders had no role in study design, collection, analysis or interpretation of data, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Burden of rare cancers in Europe

Table 1 provides incidence and survival estimates for each of the 198 rare cancers, for 63 groups of rare cancers (capital letters), for the 12 wider families in which rare cancers are hierarchically grouped, and for six common cancer groups. Hematological malignancies, rare cancers of female genital organs and of the digestive tract, and head and neck cancers were families with the highest overall incidence rates (from 15 to 28/100,000/year). Thoracic cancers, male genital and urological, endocrine organs, central nervous system (CNS) tumors and sarcomas had

overall incidence rates from 5 to 8/100,000. Rare skin cancers and non-cutaneous melanoma, and embryonal cancers were the families with the lowest rates (1.22 and 0.34 per 100,000). Overall, rare cancers accounted for 24% of all cancers diagnosed in EU28 during 2000-2007; by far the majority were solid cancers (76%). For sex-specific rare cancers, we also provide in supplementary table (see appendix p ~~xxx~~41) sex specific incidence rates.

Five-year RS of all rare cancers together was 49%, compared to 63% for all common cancers. Rare cancers also had lower survival within the families of digestive cancers (15% *vs.* 41%), female genital cancers (58% *vs.* 82%), male genital and urologic cancers (74% *vs.* 76%), skin cancers (70% *vs.* 96%) and hematological tumors (51% *vs.* 61%). The only exception was the group of thoracic cancers (13% *vs.* 10%), where common cancers included squamous cell carcinoma of the lung - with a very bad prognosis (6% after five years). Families including only rare cancers had five-year RS ranging from high, as for embryonal and endocrine organ tumors (79% and 88%), to intermediate, for sarcomas (60%), neuroendocrine (54%) and head & neck tumors (52%), and low for CNS tumors (21%).

Time trends of incidence and survival for rare cancers are shown in Figures 1 and 2. Cancers whose incidence variation fell outside the confidence interval shown in Figure 1 are listed in Table 2, with the age-standardized incidence estimates for 1999-2002 and 2003-2007, the corresponding APC and three-standard-error confidence intervals. Rare cancer dots in the plot seem to be distributed fairly symmetrically around the zero-change line, indicating no major systematic shifts in incidence. Overall there was a slight increase: the average APC for all the entities was +2.3% per year. There was a significant increase in incidence (99.8%) for 16 rare cancers, and a significant decrease for ten. Trends of rare cancers did not substantially differ from those of common cancers (data not shown), whose average annual change was +0.9%. Only prostate and skin cancers had an APC greater than 2%, while only epithelial cancers of the stomach decreased more than 2%.

Survival increased from 1999-2001 to 2005-2007 for the majority of rare cancers. The cloud of points in Figure 2 is skewed upward from the zero line, corresponding to a mean increase in survival, averaged over all the entities, of about 5.7 percent points. Twenty-four rare cancers presented significant survival increases (Table 3), while only one (other myelodysplastic syndromes) had a slight but significant decrease. Rare cancers with the largest survival increases were mainly hematological: chronic myeloid leukemia, diffuse B cell lymphoma, follicular lymphoma, precursor B/T lymphoblastic leukemia/lymphoma, and multiple myeloma. Well represented among the top tumors with increasing survival were sarcomas, specifically of the viscera, trunk, and Kaposi sarcoma. Survival increases higher than five percent points were also observed for infiltrating ductal carcinoma of the prostate (12 percent points), poorly differentiated endocrine carcinoma of the digestive system (7.5 percent points), and squamous cell carcinoma of the oropharynx (7.1 percent points). There were no major improvements for rare cancers of the colon, rectum, breast and kidney, differently from the corresponding groups of common cancers [8].

Where are rare cancers treated?

Figure 3 illustrates the extent of centralization of rare cancer treatment, presenting MAV, overall and by country, for 38 cancer groups ranked by decreasing incidence. Logarithmic scale is here used for the x-axis to made the graph readable despite the huge MAV variability (from 82 to 0.2 per year) across the considered cancers. A supplementary Table (see appendix p ~~xxx~~43) ~~Supplementary Table 1~~ gives the numbers for the graphs. Pooled MAV (Figure 3a) ranged from a maximum of 83 treatments per year for head and neck tumors to fewer than 0.5 per year for choriocarcinoma of the placenta, some embryonal and endocrine tumors. The higher the incidence, the larger the MAV of treating hospitals. The relationship between cancer incidence and MAV in the pool of countries was very strong (Pearson coefficient 0.88), though with several outliers. This was the case for epithelial tumors of the ovary, which had a higher incidence but a lower MAV than CNS tumors, whose patients seemed therefore to be more centralized than ovarian cancer patients (35 *vs.* 20 cases treated per year). Similarly, soft tissue sarcomas had a five times higher incidence, but received less centralized treatment than bone sarcomas. Treatment for for thyroid cancers, uveal melanoma and several embryonal tumors appeared to be fairly concentrated in few hospitals with relatively high volumes. In contrast, tumors of the urinary tract, gastro-entero-pancreatic neuroendocrine tumors (GEP-NET), small intestine, non-epithelial ovary

cancers, and NET of skin were treated in centers with an even lower MAV than would be expected because of their very low occurrence.

With some exceptions, country-specific patterns of MAV reflected the overall picture. Differently from what found in the other countries, the management of epithelial ovarian cancers was highly centralised In Bulgaria and Slovenia. ~~Centralization of epithelial ovarian cancers was not low in Bulgaria and Slovenia.~~ CNS patients were treated in highly centralized structures in all countries except Finland and Navarra. Treatment for uveal melanoma and retinoblastoma was not centralized in Bulgaria and, again, in Navarra. Slovenia and the Netherlands had the highest centralization patterns, while MAV for the majority of cancers was very low in Navarra.

Table 4 presents, for each country and 29 rare cancers, the annual number of cases diagnosed, the number of top-volume hospitals treating at least 75% of national cases, and the average annual numbers of treatments provided. Taking for example head and neck cancers, 3/4 of patients were centralized in two top hospitals in Slovenia (2 million population, 266 treatments per hospital per year), and 12 top hospitals in the Netherlands (17 million population, 201 treatments per hospital per year). The level of centralization was lower in the other countries, resulting in a caseload of 145 in the ten Bulgarian top hospitals, 106 in the 29 Belgian hospitals, and respectively 83, 77, and 63 in Finland, Navarra and Ireland. The Netherlands and Slovenia had the highest treatment volumes out of the 29 considered, with 12 rare cancers each.

Discussion

Rare cancers make up one quarter of all malignancies. They are a very heterogeneous group of almost 200 cancers, mostly solid, constituting from 2% of all skin cancers up to 32% of all female genital cancers. We confirmed the lower five-year survival for rare than common cancers (49% *vs.* 63%), and for all cancer families except thoracic cancers. The disadvantage persisted even after excluding common cancers with good prognosis, of prostate, breast and skin. Several factors help explain these differences: the biology of the diseases, adequacies of diagnosis and treatment, lack of effective therapies, or lack of evidence-based treatment guidelines.

A novelty of this study is the analysis of incidence and survival trends. Overall, incidence rose by 2.3% a year from 1999 up to 2007. The increase was substantial for several rare cancers (Figure 1). Some of the increase can probably be attributed to improvement in pathological diagnosis, new entity codes in the ICD-O-3 and to the time needed to adapt the coding procedures. This is the case of GIST, large cell carcinoma of ~~the~~ lung, neuroendocrine tumours and many hematological codes [9-11]. For other rare cancers, increases in incidence may be due to better pathological diagnosis, like for the neuroendocrine tumors. For thyroid carcinoma several authors have suggested an increase in over-diagnosis [12]. However, increased exposure to risk factors may explain higher incidence rates for oropharynx and anal canal squamous cell cancers due to human papillomavirus (HPV) [13,14] and for adenocarcinoma of the esophagus, perhaps due to increasing obesity or gastro-esophageal reflux [15]. The lower squamous cell carcinoma cervix incidence might reflect organised cervical screening programs. The drop in incidence for some of the rare cancers was due to the still falling prevalence of smoking [16].

RS improved by about 3% overall, slightly less than for common cancers (5.5%, data not shown), suggesting that investments were more focused on these latter. Also, over-diagnosis is expected to affect more common than rare cancers. Success was greatest for chronic myeloid leukemia (CML) with a five-year gain in survival of 21% across the study years, largely explained by the widespread use of new and more effective treatments, such as targeted treatments and more effective stem-cell transplantation [17]. For many other hematological cancers, new (targeted) drugs, combination with radiotherapy and again improvement in transplantation are responsible for the impact on prognosis [18]. Survival also improved for some groups of sarcoma (viscera, trunk and limbs) for which multidisciplinary approaches and centralization of treatments may take the credit. This may also be true for neuroendocrine tumors [19], biliary tract, liver [20] and esophageal cancers [15], for which there are now more specific and effective treatments/protocols. For esophageal cancers, earlier detection through Barrett's esophagus

surveillance practices might also contribute. For oropharyngeal cancers, the larger proportion of less aggressive tumors attributed to HPV may have influenced the survival gain [21]. For carcinoma of the thyroid and infiltrating ductal carcinoma of the prostate, early diagnosis should be the major factor. This would also have contributed to a rise in the proportion of cases that are clinically irrelevant, though this is hard to estimate [12, 22]. As found for incidence,

~~Like for incidence,~~ some of the apparent survival gains may be due to classification changes [9], such as for large cell carcinomas of the lung.

Myeloproliferative neoplasms and myelodysplastic syndromes were not considered cancers until the WHO classification was changed in 2001, and their registration started even later [9]. More in general, the increases in incidence of some rare cancers could be due to more specific diagnosis and coding by registry.

The hospital volume analysis represents the first attempt to systematically study the place of treatment of rare cancers from population-based CR data. Many potentially relevant indications can be drawn from this seldom used source of information. However, several important limitations must be recognized. Seven CRs cannot be considered as statistically representative of the whole European population. Bulgaria, Finland and Navarra only provided information on, at most, three treatments: the first surgical, systemic and radiotherapy treatments. However, we estimated from the data of the other CRs that this problem only regard about 1% of all patients.

The mean admission volume estimates, based on individual patient data and blind administrative coding of hospitals, will depend on how cancer services were organized and coded. We cannot know if, for some rare cancers and in some countries, hospitals were linked in organized networks during the study period, thus overcoming an apparent dispersion of treating structures. For example, patients with localised sarcomas or head and neck cancers were more frequently treated by small and/or peripheral hospitals [23]. If several hospitals provided different services but acted co-operatively as a single specialist center, their estimated volume will depend on

whether they were identified as a single or separate units. Our data do not allow identifying in detail specific protocols used in the considered hospitals. Hospital volume can be therefore considered as an only partial quality indicator, mainly pointing to level of experience in protocol application and general management of rare cancer patients. ~~Not all the seven CRs participating in this part of the study were able to provide the admission dates, so we could not analyse the treatment delay and timings. Bulgaria, Finland and Navarra only provided information on, at most, three treatments: the first surgical, systemic and radiotherapy treatments. However, our definition of hospital admission volume was based on one admission per treatment type per hospital, so we only lose duplicated surgical or systemic treatments done in different hospitals. We estimated from the data of the other CRs that this only happens for about 1% of all patients.~~

~~The use of individual patient data only provides a partial picture of cancer care organization in a country. We cannot exclude that, for some rare cancers and in some countries, hospitals were linked in organized networks during the study period, thus overcoming an apparent dispersion of treating structures. For example, patients with localised sarcomas or head and neck cancers were more frequently treated by small and/or peripheral hospitals [23]. In some countries several hospitals provide different services but act co-operatively as a single specialist center. Finally, seven CRs cannot be considered as statistically representative of the whole European population.~~

There are several suggestions that centralization of care improves outcome for rare cancers [24]. This is particularly true when optimal treatment requires complex surgery or high-technology radiotherapy equipment. It is beyond the scope of this paper to address the volume-survival relationship. Diagnosis and treatment in reference centers are expected to be more accurate because they benefit from large numbers of cases, which are often discussed in a multidisciplinary setting involving expert professionals. Often centralized sites are connected to research centers participating in international debates and research. Disadvantages of

centralization are the need for patients to move and the risk of a longer waiting list, with consequent discomfort and possible negative effects on outcome [25].

Sometimes, centralisation was only moderately perceived by oncologists as a solution to be endorsed for rare cancer patients.[26]

~~National cancer plans should specifically address the needs of rare cancer patients from diagnosis to treatment and palliative care, regulate their referral to centers of expertise while avoiding bottleneck effects in the designated hospitals, and include periodic evaluation of outcomes. For very rare diseases and small countries, international networks could be the best option.~~

For many of the solid rare cancers, centralization did not seem to have been completely achieved during the study period. However, most cases had been diagnosed more than ten years ago when centralization for cancer patients did not necessarily have much priority. Centralization seemed to be more widely implemented for rare cancers requiring highly specific technologies (particularly radiotherapy and nuclear medicine) and for those with long-established evidence-based guidelines for diagnosis and treatment. This was the case for many pediatric tumors, uveal melanoma, anal canal cancers, adrenal cortex cancers and, for specific surgical expertise, in CNS cancers and bone sarcomas. ~~Our data also suggest that centralization is implemented less for cancers affecting the elderly. From our data, 26% of rare cancers affect patients aged over 75 (not shown), for whom systemic therapy is often preferred to surgery more than for younger cases.~~

The degrees of centralization varied across Europe, and to a large extent were affected by the population size. In countries with a small population it is easier to concentrate patients in a single or few hospitals. High admission volumes are more likely to be achieved in reference centers in larger-population countries.

The results of this part of the study were discussed in the participating countries at dedicated meetings attended by public health planners, oncologists, surgeons, representatives of Ministries of Health and patient associations. While the general pattern of dispersion was recognised, almost all the countries were working at different levels to implement centralization and/or network-based organizations for treatment, while still following country-specific priorities [~~26~~27].

~~Belgium and the Netherlands are the two largest countries in the study.~~ In Belgium, where all cancer patients can be treated in any hospital with an oncology care program, the level of centralization was low. ~~The need was recognized to improve collaboration, centralization of care and knowledge sharing.~~ A plan is now under way for the development of hospital networks between centers of expertise ~~for rare cancers~~ and other oncology care services/programs. Centralization was already ongoing in the Netherlands, mostly for surgical treatment. This was reflected in the high admission volumes in this country for many rare cancers (see ~~Table S1~~appendix p ~~xxx~~41).

In Bulgaria rare cancer patients were operated in all hospitals with surgical departments, while radiotherapy was concentrated in 17 centers and systemic therapy in 14 oncological hospitals. A major issue remains the quality of diagnosis, mainly due to inadequate facilities ~~and abilities~~ to diagnose many complex rare cancers. The definition of national and international pathways for second opinions from expert pathologists was ~~also~~ deemed important. With this in mind, the European Reference Networks should offer a good opportunity to improve pathologist training through dedicated training schemes and fellowships across Europe. Cancer registration remains vital for monitoring progress in rare cancer diagnosis and treatment for these patients.

In Finland, more than 60% of rare cancer patients were treated in five university hospitals. Centralization in single national structures was only observed for uveal melanoma and retinoblastoma. Further centralization for other rare cancers is impeded by the spread of the

population over large areas and by administrative constraints on regional health authorities for referring cancer patients to the closest university hospital.

Irish public health authorities, during the period covered by the study, identified, a few centers to treat rare or particularly complex cancers. However, patients were not always correctly referred to them. This highlights the need for strong political commitment to ensure centralization, to make sure all rare cancer patients receive the highest quality of care.

Cancer care was highly centralized in Slovenia. In addition, the major hospitals were organized on a task-specific basis: radiotherapy was only provided by the National Cancer Center, while surgical treatment was more often done in two other major hospitals. Reducing delays in diagnosis and treatment was recognized in Slovenia as one of the major challenges in order to improve rare cancer outcomes.

Navarra is a relatively small region of Spain, a country with a highly regionalized health organisation. No hospital with national recruitment for rare cancers was operating in Navarra, and 98% of resident rare cancer patients were treated locally, the majority in the two largest regional hospitals. However, the admission volumes of Navarra hospitals are much lower than in all the other participating countries, even considering some underestimation due to unregistered patients coming from outside the region. This suggests some disadvantages in organizing rare cancer treatment on a regional/local basis.

To conclude, this is the largest study that estimates the burden of rare cancer for Europe, including trends in incidence and survival rates. It also provides indicators of rare cancer treatment management. In seven European countries we observed - with few exceptions - a low level of centralization of treatment for rare cancers. We recognise the importance of population-based cancer registries in descriptive studies like this, to ensure surveillance. However, the quality of the data needs to be improved when morphology, hospital and treatment definitions are considered. To this aim, the use of specific data quality indicators, the planning of periodic sample-based quality studies and, above all, a wider use of these variables in population based studies, with related sensitivity analysis, can be suggested. Furthermore, the international classification for cancer have to rapidly include the new entities based on molecular and genomic categorization. The latter is a necessary condition for updating a new rare cancers list.

The European network of cancer registries (ENCR) should work to boost these quality improvements and make wider use of the data on rare cancers. The Joint Action of Rare Cancers [~~27~~28] and the European Network for Rare Diseases will profit from these data, which are also useful for national and European policies to organize care for rare cancer patients better. The RARECAREnet project website includes a search tool with data for all the countries that contributed data [3].

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Author contributions

GG, RC and AT designed the study, and wrote the article. RC, LB, SM and RD did the statistical analyses. LB, RD, SM, EA, HC,ND, MKL, SS, JMVZ, LVE, OV, MPZ, LAA, FB, KI,RO and CSA revised the paper and contributed to data interpretation. All authors reviewed and approved the final version. Members of the working group collected data.

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Table 1. Estimates of incidence and survival for rare and common cancers, together with expected number of new cases

Family	Cancer entity	Crude Incidence Rate per 100,000 per year	95% Confidence Interval lower	upper	Number of observed cases in 83 CRs in 2000-2007	Estimated new cases at 2013 in EU (28)	Five-year relative survival (%)	95% Confidence Interval lower	upper	Number of observed cases in 94 CRs in 2000-2007
RARE CANCERS										
Head and neck cancers		**18.82**	16.76	16.89	**263,565**	**84,989**	52.1	51.8	52.3	254,563
	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	0.45	0.44	0.46	7,046	2,282	47.3	45.8	48.8	6,867
	Squamous cell carcinoma with variants of nasal cavity and sinuses	0.35	0.34	0.36	5,465	1,770	49.5	47.8	51.2	5,444
	Lymphoepithelial carcinoma of nasal cavity and sinuses	0.00	0.00	0.00	31	10	70.8	50.7	99.0	31
	Undifferentiated carcinoma of nasal cavity and sinuses	0.02	0.02	0.02	286	93	30.5	24.3	38.2	283
	Intestinal type adenocarcinoma of nasal cavity and sinuses	0.00	0.00	0.00	42	14	65.0	48.9	86.4	42
	EPITHELIAL TUMOURS OF NASOPHARYNX	0.47	0.46	0.49	7,439	2,580	48.9	47.5	50.2	7,276
	Squamous cell carcinoma with variants of nasopharynx	0.36	0.35	0.37	5,613	1,941	48.5	47.0	50.1	5,589
	Papillary adenocarcinoma of nasopharynx	0.00	0.00	0.00	17	6	58.7	36.2	95.3	17
	EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	1.39	1.37	1.41	21,794	7,059	62.8	62.0	63.7	21,364
	Epithelial tumours of major salivary glands	0.96	0.95	0.98	15,053	4,876	60.8	59.8	61.8	14,703
	Salivary gland type tumours of head and neck	0.43	0.42	0.44	6,741	2,183	67.1	65.7	68.6	6,683
	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	6.33	6.29	6.37	99,176	31,545	52.0	51.6	52.4	96,793
	Squamous cell carcinoma with variants of hypopharynx	1.27	1.25	1.28	19,828	6,422	25.1	24.4	25.9	19,878
	Squamous cell carcinoma with variants of larynx	4.61	4.58	4.64	72,210	23,389	60.5	60.1	61.0	71,928
	EPITHELIAL TUMOURS OF OROPHARYNX	3.32	3.29	3.35	52,017	16,848	40.9	40.4	41.4	50,843
	Squamous cell carcinoma with variants of oropharynx	3.12	3.09	3.14	48,812	15,810	41.3	40.8	41.8	48,401
	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	4.78	4.75	4.81	74,890	24,257	56.7	56.2	57.1	73,101
	Squamous cell carcinoma with variants of oral cavity	3.51	3.48	3.54	54,931	17,792	48.0	47.5	48.6	54,229
	Squamous cell carcinoma with variants of lip	1.02	1.00	1.04	15,984	5,177	89.5	88.5	90.5	15,899

	EPITHELIAL TUMOURS OF EYE AND ADNEXA	0.04	0.04	0.05	679	247	80.6	75.9	85.6	673
	Squamous cell carcinoma with variants of eye and adnexa	0.03	0.02	0.03	421	136	88.9	83.0	95.2	422
	Adenocarcinoma with variants of eye and adnexa	0.01	0.01	0.01	134	43	58.7	49.1	70.1	134
	EPITHELIAL TUMOURS OF MIDDLE EAR	0.03	0.03	0.04	524	170	44.1	38.5	49.6	488
	Squamous cell carcinoma with variants middle ear	0.02	0.02	0.03	377	122	37.6	31.8	44.4	370
	Adenocarcinoma with variants of middle ear	0.00	0.00	0.00	50	16	83.8	70.5	99.5	50
Digestive rare cancers		**21.94**	21.86	22.01	**343635**	**112,351**	**15.3**	15.2	15.5	**321,375**
	EPITHELIAL TUMOURS OF OESOPHAGUS	7.81	7.77	7.85	122,344	40068	11.98	11.8	12.2	119,522
	Squamous cell carcinoma with variants of oesophagus	3.36	3.33	3.39	52,597	17,036	11.7	11.3	12.0	53,225
	Adenocarcinoma with variants of oesophagus	3.26	3.24	3.29	51,138	16,564	13.9	13.5	14.2	51,250
	Salivary gland type tumours of oesophagus	0.00	0.00	0.01	63	20	13.7	6.4	29.0	64
	Undifferentiated carcinoma of oesophagus	0.04	0.04	0.05	695	225	6.8	4.9	9.4	712
	RARE EPITHELIAL TUMOURS OF STOMACH	0.33	0.32	0.34	5,146	1,886	15.9	14.7	17.1	5,157
	Squamous cell carcinoma with variants of stomach	0.12	0.11	0.12	1,807	585	17.5	15.6	19.7	1,800
	Salivary gland-type tumours of stomach	0.00	0.00	0.00	39	13	25.1	12.7	49.9	40
	Undifferentiated carcinoma of stomach	0.21	0.20	0.22	3,300	1,069	14.9	13.5	16.4	3,317
	EPITHELIAL TUMOURS OF SMALL INTESTINE	0.77	0.76	0.79	12,132	3,930	27.3	26.3	28.3	11,544
	Adenocarcinoma with variants of small intestine	0.59	0.58	0.60	9,219	2,986	27.9	26.8	29.0	9,193
	Squamous cell carcinoma with variants of small intestine	0.01	0.01	0.01	133	43	34.8	26.8	45.3	133
	RARE EPITHELIAL TUMOUR OF COLON	0.13	0.13	0.14	2,074	737	54.8	52.0	57.7	2,075
	Squamous cell carcinoma with variants of colon	0.03	0.02	0.03	400	130	37.1	31.8	43.4	395
	Fibromixoma and low grade mucinous adenocarcinoma of the appendix	0.11	0.10	0.11	1,674	542	58.8	55.7	62.1	1,680
	RARE EPITHELIAL TUMOURS OF RECTUM	0.11	0.11	0.12	1,764	635	47.2	44.4	50.2	1,777
	Squamous cell carcinoma with variants of rectum	0.11	0.11	0.12	1,764	571	47.2	44.4	50.2	1,777
	EPITHELIAL TUMOURS OF ANAL CANAL	1.16	1.14	1.18	18,155	5,880	56.5	55.5	57.4	18,020
	Squamous cell carcinoma with variants of anal canal	0.81	0.80	0.82	12,691	4,111	63.0	61.9	64.1	12,847
	Adenocarcinoma with variants of anal canal	0.25	0.25	0.26	3,970	1,286	41.9	39.9	43.9	3,945
	Paget s disease of anal canal	0.00	0.00	0.00	21	7	62.9	38.0	104.0	21

	RARE EPITHELIAL TUMOURS OF PANCREAS	0.07	0.07	0.08	1,159	414	20.2	17.4	23.3	1,116
	Squamous cell carcinoma with variants of pancreas	0.02	0.02	0.03	361	117	5.9	3.6	9.6	347
	Acinar cell carcinoma of pancreas	0.03	0.03	0.03	449	145	19.0	14.8	24.3	427
	Mucinous cystadenocarcinoma of pancreas	0.01	0.01	0.01	109	35	35.9	26.3	49.0	106
	Intraductal papillary mucinous carcinoma invasive of pancreas	0.01	0.01	0.01	173	56	31.8	23.6	42.9	171
	Solid pseudopapillary carcinoma of pancreas	0.00	0.00	0.00	44	14	67.7	52.8	86.8	42
	Serous cystadenocarcinoma of pancreas	0.00	0.00	0.00	4	1	NE	NE	NE	4
	Carcinoma with osteoclast-like giant cells of pancreas	0.00	0.00	0.00	19	6	NE	NE	NE	19
	EPITHELIAL TUMOURS OF LIVER AND INTRAEPATIC BILE TRACT (IBT)	7.10	7.06	7.14	111,271	36,261	10.1	9.9	10.3	98,765
	Hepatocellular carcinoma of Liver and IBT	3.22	3.19	3.25	50,461	16,344	14.0	13.7	14.4	46,896
	Hepatocellular carcinoma, fibrolamellar of liver and IBT	0.02	0.02	0.03	387	125	28.1	23.3	33.8	390
	Cholangiocarcinoma of IBT	0.97	0.95	0.99	15,201	4,924	6.0	5.6	6.6	13,845
	Adenocarcinoma with variants of liver and IBT	0.41	0.40	0.42	6,457	2,091	6.6	5.9	7.4	6,311
	Undifferentiated carcinoma of liver and IBT	0.02	0.01	0.02	240	78	2.7	1.2	6.4	219
	Squamous cell carcinoma with variants of liver and IBT	0.01	0.01	0.01	147	48	14.6	9.1	23.4	143
	Bile duct cystadenocarcinoma of IBT	0.00	0.00	0.00	38	12	23.6	11.5	48.5	34
	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	4.44	4.41	4.48	69,590	22,540	13.6	13.2	13.9	63,889
	Adenocarcinoma with variants of gallbladder	1.35	1.33	1.36	21,085	6,830	14.5	14.0	15.1	20,338
	Adenocarcinoma with variants of EBT	1.44	1.42	1.46	22,510	7,291	19.2	18.6	19.8	22,234
	Squamous cell carcinoma of gallbladder and EBT	0.03	0.03	0.03	496	161	8.8	6.3	12.3	476
Thoracic rare cancers		**6.80**	6.76	6.84	**106573**	**37,277**	**13.4**	13.1	13.6	**104,670**
	EPITHELIAL TUMOUR OF TRACHEA	0.11	0.11	0.12	1,771	574	18.0	16.0	20.3	1,697
	Squamous cell carcinoma with variants of trachea	0.06	0.06	0.07	1,017	329	12.2	10.0	14.9	1,008
	Adenocarcinoma with variants of trachea	0.01	0.01	0.01	164	53	15.7	10.3	24.0	158
	Salivary gland type tumours of trachea	0.01	0.01	0.01	175	57	70.1	62.0	79.2	174
	RARE EPITHELIAL TUMOUR OF LUNG	4.37	4.34	4.40	68,452	24,930	14.9	14.6	15.2	67,936
	Adenosquamous carcinoma of lung	0.29	0.29	0.30	4,607	1,492	21.9	20.5	23.4	4,566
	Large cell carcinoma of lung	3.81	3.78	3.84	59,714	19,342	13.9	13.5	14.2	59,332

	Salivary gland type tumours of lung	0.06	0.05	0.06	879	285	40.4	36.8	44.4	866
	Sarcomatoid carcinoma of lung	0.21	0.20	0.22	3,255	1,054	17.5	16.0	19.2	3,183
	EPITHELIAL TUMOURS OF THYMUS	0.18	0.17	0.19	2,795	905	64.3	62.1	66.6	2,729
	Malignant thymoma	0.14	0.14	0.15	2,268	735	69.3	67.0	71.8	2,248
	Squamous cell carcinoma of thymus	0.01	0.01	0.01	114	37	40.4	30.4	53.7	112
	Undifferentiated carcinoma of thymus	0.00	0.00	0.00	36	12	13.3	5.1	34.8	36
	Lymphoepithelial carcinoma of thymus	0.00	0.00	0.00	12	4	55.0	29.2	103.6	11
	Adenocarcinoma with variants of thymus	0.00	0.00	0.00	45	15	37.3	21.7	64.1	44
	MALIGNANT MESOTHELIOMA	2.14	2.12	2.16	33,552	10,868	5.3	4.9	5.6	32,330
	Mesothelioma of pleura and pericardium	1.83	1.81	1.85	28,676	9,288	4.6	4.2	4.9	27,893
	Mesothelioma of peritoneum and tunica vaginalis	0.13	0.13	0.14	2,065	669	13.2	11.5	15.1	1,965
Female genital rare cancers		**22.73**	22.66	22.81	**356151**	**113,796**	**57.7**	57.5	57.9	**347,015**
	RARE EPITHELIAL TUMOURS OF BREAST	4.12	4.09	4.16	64,605	22,980	91.4	91.0	91.8	64,368
	Mammary Paget's disease of breast	0.41	0.40	0.42	6,488	2,101	85.9	84.6	87.3	6,508
	Special types of adenocarcinoma of breast	3.06	3.04	3.09	48,012	15,551	95.2	94.8	95.6	47,974
	Metaplastic carcinoma of breast	0.10	0.10	0.11	1,576	510	65.0	61.9	68.3	1,583
	Salivary gland type tumours of breast	0.06	0.05	0.06	868	281	90.9	87.6	94.2	870
	Epithelial tumour of male breast	0.52	0.51	0.53	8,098	5,376	77.0	75.5	78.5	7,882
	RARE EPITHELIAL TUMOURS OF CORPUS UTERI	0.70	0.69	0.72	11,038	3,932	44.3	43.2	45.5	11,013
	Squamous cell carcinoma with variants of corpus uteri	0.06	0.06	0.07	1,003	325	58.2	54.6	62.1	989
	Adenoid cystic carcinoma of corpus uteri	0.00	0.00	0.00	5	2	64.1	31.3	131.1	5
	Clear cell adenocarcinoma, NOS of corpus uteri	0.16	0.16	0.17	2,527	819	58.6	56.2	61.2	2,532
	Serous (papillary) carcinoma of corpus uteri	0.08	0.07	0.08	1,227	397	40.0	36.5	43.9	1,225
	Mullerian mixed tumour of corpus uteri	0.40	0.39	0.41	6,276	2,033	36.9	35.5	38.4	6,263
	EPITHELIAL TUMOURS OF CERVIX UTERI	6.28	6.24	6.32	98,321	28,898	65.4	65.1	65.8	96,821
	Squamous cell carcinoma with variants of cervix uteri	4.73	4.70	4.76	74,105	24,003	66.8	66.5	67.2	73,810
	Adenocarcinoma with variants of cervix uteri	0.91	0.89	0.92	14,252	4,616	67.4	66.5	68.3	14,221
	Undifferentiated carcinoma of cervix uteri	0.03	0.03	0.03	480	155	35.3	30.9	40.4	478

	Mullerian mixed tumour of cervix uteri	0.02	0.01	0.02	257	83	34.3	28.1	41.7	256
	EPITHELIAL TUMOUR OF OVARY AND FALLOPPIAN TUBE	9.38	9.33	9.43	146,908	45,382	37.5	37.2	37.8	141,240
	Adenocarcinoma with variants of ovary	5.95	5.92	5.99	93,263	30,208	38.7	38.3	39.1	92,814
	Mucinous adenocarcinoma of ovary	0.77	0.76	0.78	12,066	3,908	59.9	58.9	60.9	12,010
	Clear cell adenocarcinoma of ovary	0.30	0.29	0.31	4,753	1,540	55.5	53.8	57.2	4,761
	Primary peritoneal serous/papillary carcinoma of ovary	0.08	0.08	0.09	1,280	415	21.9	19.1	25.2	1,280
	Mullerian mixed tumour of ovary	0.14	0.14	0.15	2,255	730	21.4	19.5	23.6	2,242
	Adenocarcinoma with variant of falloppian tube	0.17	0.16	0.18	2,683	869	59.1	56.8	61.6	2,672
	NON EPITHELIAL TUMOURS OF OVARY	0.25	0.25	0.26	3977	1288	82.0	80.6	83.5	3,970
	Sex cord tumours of ovary	0.13	0.12	0.13	2,006	650	78.8	76.5	81.1	1,998
	Malignant/Immature teratomas of ovary	0.05	0.05	0.06	833	270	83.4	80.6	86.3	829
	Germ cell tumour of ovary	0.07	0.07	0.08	1,138	369	86.6	84.4	88.8	1,143
	EPITHELIAL TUMOURS OF VULVA AND VAGINA	1.97	1.95	2.00	30938	11215	58.1	57.3	58.8	30,238
	Squamous cell carcinoma with variants of vulva and vagina	1.69	1.67	1.71	26,422	8,558	59.8	59.0	60.7	26,277
	Adenocarcinoma with variants of vulva and vagina	0.07	0.07	0.08	1,120	363	45.8	42.3	49.6	1,112
	Paget s disease of vulva and vagina	0.05	0.04	0.05	746	242	88.0	83.7	92.6	744
	Undifferentiated carcinoma of vulva and vagina	0.01	0.00	0.01	85	28	25.6	15.8	41.6	85
	TROPHOBLASTIC TUMOUR OF PLACENTA	0.02	0.02	0.03	363	100	89.3	85.3	92.2	361
	Choriocarcinoma of placenta	0.02	0.02	0.02	352	114	89.8	86.5	93.3	350
Male genital and urogenital rare cancers		**7.09**	7.05	7.14	**111128**	**38,138**	**73.64**	73.3	74.0	**109,102**
	RARE EPITHELIAL TUMOURS OF PROSTATE	0.60	0.59	0.61	9,437	3,563	75.4	74.0	76.9	9,291
	Squamous cell carcinoma with variants of prostate	0.02	0.02	0.02	291	94	41.1	34.1	49.5	287
	Infiltrating duct carcinoma of prostate	0.51	0.50	0.53	8,064	2,612	78.7	77.2	80.3	7,945
	Transitional cell carcinoma of prostate	0.06	0.06	0.07	960	311	57.7	53.4	62.4	941
	Salivary gland type tumours of prostate	0.01	0.01	0.01	122	40	78.5	64.4	95.7	118
	TESTICULAR AND PARATESTICULAR CANCERS	3.29	3.27	3.32	51605	16061	94.9	94.7	95.2	51,011
	Paratesticular adenocarcinoma with variants	0.00	0.00	0.00	22	7	82.5	65.3	104.1	22

	Non seminomatous testicular cancer	1.27	1.25	1.28	19,835	6,425	92.9	92.5	93.3	19,714
	Seminomatous testicular cancer	1.82	1.80	1.84	28,516	9,236	97.5	97.3	97.8	28,326
	Spermatocytic seminoma	0.03	0.03	0.03	502	163	95.3	91.8	99.0	502
	Teratoma with malignant transformation	0.00	0.00	0.00	20	6	91.4	78.6	106.2	20
	Testicular sex cord cancer	0.02	0.02	0.02	340	110	82.3	77.3	87.6	337
	EPITHELIAL TUMOURS OF PENIS	0.66	0.65	0.67	10368	3887	67.5	66.2	68.9	10,210
	Squamous cell carcinoma with variants of penis	0.62	0.60	0.63	9,646	3,124	68.9	67.5	70.2	9,621
	Adenocarcinoma with variants of penis	0.01	0.00	0.01	88	29	49.0	36.2	66.4	86
	RARE EPITELIAL TUMOURS OF KIDNEY	0.05	0.04	0.05	723	261	18.8	15.8	22.4	704
	Squamous cell carcinoma spindle cell type of kidney	0.01	0.01	0.01	190	62	22.0	16.0	30.2	190
	Squamous cell carcinoma with variants of kidney	0.03	0.03	0.04	533	173	17.7	14.4	21.7	514
	EPITHELIAL TUMOURS OF PELVIS AND URETER	1.58	1.57	1.60	24826	9187	48.8	48.0	49.7	24,017
	Transitional cell carcinoma of pelvis and ureter	1.41	1.39	1.43	22,099	7,158	51.3	50.4	52.2	21,607
	Squamous cell carcinoma with variants of pelvis and ureter	0.02	0.02	0.03	372	121	15.0	11.2	20.2	366
	Adenocarcinoma with variants of pelvis and ureter	0.02	0.02	0.02	326	106	43.0	36.7	50.5	320
	EPITHELIAL TUMOURS OF URETHRA	0.13	0.13	0.14	2077	784	44.5	41.6	47.5	2,050
	Transitional cell carcinoma of urethra	0.09	0.08	0.09	1,390	450	42.9	39.5	46.7	1,387
	Squamous cell carcinoma with variants of urethra	0.02	0.02	0.02	329	107	51.1	44.6	58.5	329
	Adenocarcinoma with variants of urethra	0.01	0.01	0.01	190	62	52.0	43.2	62.6	189
	RARE EPITHELIAL TUMOURS OF BLADDER	0.65	0.64	0.67	10226	3819	32.3	31.2	33.5	10,152
	Squamous cell carcinoma with variants of bladder	0.36	0.35	0.36	5,566	1,803	24.3	22.9	25.7	5,534
	Adenocarcinoma with variants of bladder	0.30	0.29	0.31	4,653	1,507	41.9	40.1	43.8	4,614
	Salivary gland type tumours of bladder	0.00	0.00	0.00	7	2	NE	NE	NE	7
	EXTRAGONADAL GERM CELL TUMOURS	0.12	0.11	0.12	1,862	576	69.6	67.3	71.8	1,851
	Non seminomatous germ cell tumours	0.06	0.05	0.06	915	296	62.5	59.2	66.0	909
	Seminomatous germ cell tumors	0.01	0.01	0.01	130	42	85.9	79.1	93.3	130
	Germ cell tumors of CNS	0.04	0.03	0.04	574	186	82.5	79.2	85.9	572
Neuroendocrine tumours		**3.51**	3.43	3.58		**19587**	**53.5**	53.0	54.1	**54,331**
	NEUROENDOCRINE TUMOURS	3.51	3.48	3.54	54942	19587	53.5	53.0	54.1	54,331

	GEP, well diff not funct endocrine carcinoma of pancreas and digestive tract	1.01	1.00	1.03	15,852	5,134	72.0	71.1	73.0	15,656
	GEP, well diff funct endocrine carcinoma of pancreas and digestive tract	0.03	0.02	0.03	411	133	61.3	55.9	67.3	407
	GEP, poorly differentiated endocrine carcinoma	0.67	0.65	0.68	10,421	3,375	35.0	33.9	36.2	10,456
	GEP, mixed endocrine-exocrine carcinoma	0.01	0.01	0.01	147	48	25.9	18.2	37.0	141
	Endocrine carcinoma of thyroid gland	0.24	0.23	0.25	3,796	1,230	83.6	82.1	85.2	3,793
	Neuroendocrine carcinoma of skin	0.19	0.19	0.20	3,024	979	55.9	53.2	58.7	2,997
	Typical and atypical carcinoid of the lung	0.39	0.38	0.40	6,160	1,995	81.1	79.9	82.5	6,058
	Neuroendocrine carcinoma of other sites	0.90	0.89	0.92	14,120	4,573	23.9	23.0	24.8	13,958
	Pheochromocytoma, malignant	0.04	0.04	0.04	650	211	70.1	65.9	74.5	612
	Paraganglioma	0.02	0.02	0.02	347	112	56.3	50.6	62.6	342
Cancers of the endocrine organs		**5.35**	5.32	5.39	**83836**	**28,322**	**88.08**	87.8	88.4	**82,523**
	CARCINOMAS OF PITUITARY GLAND	**0.04**	0.03	0.04	582	206	63.7	58.9	69.0	511
	Carcinoma of pituitary gland	0.04	0.03	0.04	582	206	63.7	58.9	69.0	511
	CARCINOMAS OF THYROID GLAND	**5.07**	5.03	5.10	79,418	26,768	90.5	90.2	90.8	78,533
	Carcinoma of thyroid gland	5.07	5.03	5.11	79,420	26,768	90.5	90.2	90.8	78,533
	CARCINOMAS OF PARATHYROID GLAND	**0.03**	0.02	0.03	410	143	80.8	75.8	86.2	395
	Carcinoma of parathyroid gland	0.03	0.02	0.03	410	143	80.8	75.8	86.2	395
	CARCINOMA OF ADRENAL GLAND	**0.22**	0.21	0.23	3,424	1,205	32.1	30.2	34.0	3,103
	Carcinoma of adrenal gland	0.22	0.21	0.23	3,424	1,205	32.1	30.2	34.0	3,103
Sarcomas		**5.86**	5.83	6.00	**91878**	**31,916**	**59.53**	57.4	58.2	**90,568**
	SOFT TISSUE SARCOMA	4.71	4.68	4.74	73,795	25,851	56.7	56.3	57.1	72,696
	Soft tissue sarcoma of head and neck	0.26	0.25	0.27	4,087	1,324	59.8	57.7	61.8	4,062
	Soft tissue sarcoma of limbs	1.10	1.08	1.11	17,178	5,564	67.7	66.8	68.6	17,094
	Soft tissue sarcoma of superficial trunk	0.50	0.49	0.51	7,813	2,531	48.1	46.8	49.5	7,723
	Soft tissue sarcoma of mediastinum	0.03	0.03	0.03	465	151	23.4	19.3	28.3	457
	Soft tissue sarcoma of heart	0.01	0.01	0.02	216	70	14.4	9.8	21.0	203
	Soft tissue sarcoma of breast	0.18	0.18	0.19	2,865	928	74.5	72.5	76.5	2,864
	Soft tissue sarcoma of uterus	0.55	0.54	0.56	8,657	2,804	52.0	50.8	53.2	8,568

	Other soft tissue sarcomas of genitourinary tract	0.20	0.19	0.21	3,160	1,024	50.4	48.3	52.5	3,107
	Soft tissue sarcoma of viscera	0.38	0.37	0.39	6,004	1,945	42.1	40.6	43.6	5,915
	Soft tissue sarcoma of paratestis	0.03	0.03	0.04	510	165	87.2	82.2	92.4	510
	Soft tissue sarcoma of retroperitoneum and peritoneum	0.31	0.30	0.32	4,911	1,591	38.8	37.1	40.5	4,854
	Soft tissue sarcoma of pelvis	0.20	0.19	0.20	3,090	1,001	47.4	45.3	49.6	3,064
	Soft tissue sarcoma of skin	0.30	0.29	0.31	4,737	1,534	90.2	88.8	91.7	4,728
	Soft tissue sarcoma of paraorbit	0.01	0.01	0.01	117	38	63.3	52.9	75.7	115
	Soft tissue sarcoma of brain and other parts of nervous system	0.17	0.17	0.18	2,723	882	54.5	52.3	56.7	2,695
	Embryonal rhabdomyosarcoma of soft tissue	0.05	0.05	0.06	836	271	66.2	62.8	69.8	825
	Alveolar rhabdomyosarcoma of soft tissue	0.03	0.03	0.04	519	168	36.0	31.7	40.8	515
	Ewing's sarcoma of soft tissue	0.06	0.06	0.07	998	323	44.9	41.5	48.5	992
	BONE SARCOMA	0.85	0.84	0.87	13,376	4,382	58.6	57.6	59.6	13,216
	Osteogenic sarcoma	0.21	0.21	0.22	3,330	1,079	51.4	49.5	53.4	3,282
	Chondrogenic sarcomas	0.26	0.25	0.27	4,107	1,330	70.0	68.2	71.7	4,060
	Notochordal sarcomas, chordoma	0.07	0.07	0.08	1,145	371	62.5	58.2	67.2	755
	Vascular sarcomas	0.01	0.01	0.01	129	42	45.1	36.4	55.9	129
	Ewing's sarcoma	0.12	0.12	0.13	1,943	629	52.8	50.4	55.3	1,932
	Epithelial tumours, adamantinoma	0.01	0.01	0.02	213	69	87.2	81.0	93.9	210
	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0.02	0.02	0.02	304	98	46.2	40.1	53.1	302
	GASTROINTESTINAL STROMAL SARCOMA	0.30	0.29	0.31	4706	1683	72.3	70.4	74.1	4,781
	Gastrointestinal stromal sarcoma	0.30	0.29	0.31	4,706	1,524	72.3	70.4	74.1	4,781
Cancers of the central nervous system (CNS)		**7.56**	7.51	8.00	**118391**	**36,343**	**21.3**	21.0	21.6	**111,838**
	TUMOURS OF CENTRAL NERVOUS SYSTEM (CNS)**	7.36	7.32	7.40	115,289	35,339	20.3	20.0	20.6	108,752
	Astrocytic tumours of CNS	4.99	4.95	5.02	78,118	25,303	15.0	14.8	15.3	77,195
	Oligodendroglial tumours of CNS	0.39	0.38	0.40	6,148	1,991	51.8	50.4	53.3	6,124
	Ependymal tumours of CNS	0.21	0.20	0.21	3,212	1,040	72.7	71.0	74.5	3,190
	Choroid plexus carcinoma of CNS	0.01	0.01	0.01	98	32	57.7	48.3	68.8	95

	Malignant meningiomas	0.16	0.16	0.17	2,564	830	61.1	58.8	63.4	2,509
	EMBRYONAL TUMORS OF CNS	0.20	0.19	0.21	3,102	1,005	56.1	54.2	58.1	3,092
	Embryonal tumors of CNS	0.20	0.19	0.21	3,102	1,005	56.1	54.2	58.1	3,092
Rare skin cancers and non-cutaneous melanoma		**1.22**	1.18	1.25		**7,086**	**70.2**	69.3	71.1	**21,637**
	MALIGNANT MELANOMA OF MUCOSA	0.15	0.14	0.15	2,279	738	20.3	18.2	22.6	2,277
	Malignant melanoma of mucosa	0.15	0.14	0.15	2,279	738	20.3	18.3	22.6	2,277
	MALIGNANT MELANOMA OF UVEA	0.70	0.69	0.72	11,022	3,570	71.0	69.8	72.2	10,872
	Malignant melanoma of uvea	0.70	0.69	0.72	11,022	3,570	71.0	69.8	72.2	10,872
	ADNEXAL CARCINOMA OF SKIN	0.30	0.29	0.31	4,684	1,517	86.1	83.9	88.0	4,661
	Adnexal carcinoma of skin	0.30	0.29	0.31	4,684	1,517	86.1	83.9	88.0	4,661
	KAPOSI'S SARCOMA	0.25	0.24	0.26	3,893	1,261	78.9	77.0	80.7	3,830
	Kaposi's sarcoma	0.25	0.24	0.26	3,893	1,261	78.9	77.1	80.8	3,830
Embrional tumours		**0.34**	0.33	0.35	**5363**	**1,822**	78.6	77.4	79.8	5,239
	NEUROBLASTOMA AND GANGLIONEUROBLASTOMA	0.10	0.10	0.11	1566	499	64.6	62.1	67.3	1,553
	Neuroblastoma e ganglioneuroblastoma	0.10	0.10	0.11	1,566	507	64.6	62.1	67.3	1,553
	NEPHROBLASTOMA	0.13	0.12	0.13	1,965	636	88.2	86.6	89.7	1,936
	Nephroblastoma	0.13	0.12	0.13	1,965	636	88.2	86.6	89.7	1,936
	RETINOBLASTOMA	0.05	0.05	0.06	860	279	96.5	95.1	97.9	801
	Retinoblastoma	0.05	0.05	0.06	860	279	96.5	95.1	97.9	801
	HEPATOBLASTOMA	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	Hepatoblastoma	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	PLEUROPULMONARY BLASTOMA	0.02	0.02	0.03	357	116	76.8	72.2	81.7	352
	Pleuropulmonary blastoma	0.00	0.00	0.00	9	3	53.5	28.3	101.1	9
	PANCREATOBLASTOMA	0.00	0.00	0.00	9	3	53.5	28.3	101.1	9
	Pancreatoblastoma	0.00	0.00	0.00	39	13	34.3	20.7	56.9	35
	OLFACTORY NEUROBLASTOMA	0.00	0.00	0.00	39	13	34.3	20.7	56.9	35
	Olfactory neuroblastoma	0.03	0.03	0.03	498	161	64.0	59.2	69.2	489

	ODONTOGENIC MALIGNANT TUMOURS	0.03	0.03	0.03	498	161	64.0	59.2	69.2	489
	Odontogenic malignant tumours	0.00	0.00	0.01	69	22	61.6	49.0	77.5	69
Haematological rare malignancies		**27.73**	27.65	27.82	**434469**	**156,099**	**50.5**	50.3	50.7	**423,741**
	RARE LYMPHOID DISEASES	18.09	18.02	18.16	283,399	100,343	55.8	55.5	56.0	279,794
	Hodgkin lymphoma, classical	2.46	2.44	2.49	38,588	12,499	81.4	80.9	81.8	38,389
	Hodgkin lymphoma nodular lymphocyte predominance	0.09	0.09	0.10	1,483	480	93.6	91.8	95.3	1,507
	Precursor B/T lymphoblastic leuk/lymphoma (and Burkitt leukemia/lymphoma)	1.46	1.44	1.47	22,795	7,383	58.1	57.4	58.8	22,496
	T cutaneous lymphoma (Sezary syn, Mycosis fung)	0.35	0.34	0.36	5,526	1,790	81.5	80.0	83.1	5,482
	Other T cell lymphomas and NK cell neoplasms	0.62	0.60	0.63	9,656	3,128	39.0	37.9	40.2	9,635
	Diffuse B lymphoma	4.32	4.29	4.35	67,645	21,910	53.4	52.9	53.9	67,907
	Follicular B lymphoma	2.19	2.17	2.22	34,346	11,125	77.0	76.4	77.6	34,545
	Hairy cell leukaemia	0.28	0.27	0.29	4,375	1,417	89.8	88.3	91.3	4,387
	Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	5.71	5.67	5.75	89,440	28,970	35.3	34.8	35.7	86,496
	Mantle cell lymphoma	0.56	0.55	0.57	8,748	2,834	44.0	42.6	45.4	8,797
	Prolymphocytic leukaemia, B cell	0.05	0.05	0.06	804	260	30.8	26.9	35.2	788
	ACUTE MYELOID LEUKEMIA AND RELATED PRECURSOR NEOPLASMS	3.81	3.77	3.84	59,608	21,557	19.2	18.8	19.6	56,709
	Acute promyelocytic leukemia (AML with t(15;17) with variants	0.12	0.11	0.13	1,876	608	63.2	60.8	65.7	1,880
	Acute myeloid leukemia	3.50	3.47	3.53	54,789	17,746	17.5	17.1	17.8	52,305
	MYELOPROLIFERATIVE NEOPLASMS	3.31	3.28	3.34	51888	18805	68.3	67.7	68.9	50,624
	Chronic myeloid leukemia	1.12	1.10	1.13	17,473	5,660	54.9	54.0	55.9	16,599
	Other myeloproliferative neoplasms	2.17	2.14	2.19	33,954	10,998	75.0	74.3	75.7	33,599
	Mast cell tumour	0.03	0.03	0.03	461	149	71.4	66.2	77.1	454
	MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	2.47	2.45	2.50	38,738	15,116	31.1	30.5	31.8	37,792
	Myelodysplastic syndrome with 5q syndrome	0.01	0.01	0.01	156	51	48.0	38.3	60.3	178
	Other myelodysplastic syndrome	2.14	2.12	2.16	33,542	10,864	32.2	31.5	32.9	32,576
	Chronic Myelomonocytic leukemia	0.29	0.28	0.30	4,542	1,471	21.3	19.8	23.0	4,575
	Atypical chronic myeloid leukemia BCR/ABL negative	0.02	0.01	0.02	239	77	28.2	21.7	36.5	248

	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	0.05	0.05	0.06	828	278	59.9	56.1	63.9	817
	Histiocytic malignancies	0.04	0.04	0.05	656	212	63.4	59.4	67.8	645
	Lymph node accessory cell tumors	0.01	0.01	0.01	172	56	45.6	37.1	56.0	172
All rare tumours	**ALL RARE TIER2 TUMOURS**	**114.99**	**114.82**	**115.16**	**1,801,443**	636753	48.5	48.4	48.6	**1,751,601**

COMMON CANCERS

Digestive common tumours		91.80	91.65	91.95	1,438,094	**490,051**	**41.4**	41.3	45.8	**1365575**
	EPITHELIAL TUMOURS OF STOMACH	17.10	17.03	17.16	267,832	92,067	21.2	21.0	21.4	253,439
	Adenocarcinoma with variants of stomach	14.18	14.12	14.24	222,145	71,954	22.7	22.5	22.9	221,604
	EPITHELIAL TUMOUR OF COLON	43.88	43.77	43.98	687,386	234,319	54.2	54.0	54.4	664,118
	Adenocarcinoma with variants of colon	38.85	38.75	38.95	608,637	197,139	57.9	57.7	58.0	604,459
	EPITHELIAL TUMOURS OF RECTUM	17.98	17.92	18.05	281,697	95,187	53.8	53.6	54.1	276,024
	Adenocarcinoma with variants of rectum	16.45	16.39	16.52	257,723	83,477	55.8	55.6	56.1	258,469
	EPITHELIAL TUMOURS OF PANCREAS	12.84	12.79	12.90	201,179	68,478	4.1	4.0	4.2	182,579
	Adenocarcinoma with variants of pancreas	7.96	7.92	8.01	124,744	40,405	4.1	4.0	4.2	119,154
Thoracic common tumours		53.02	52.91	53.14	830,611	281,332	**10.1**	10.0	10.2	779,539
	EPITHELIAL TUMOUR OF LUNG	53.02	52.91	53.14	830,611	281,332	10.1	10.0	10.2	779,539
	Squamous cell carcinoma with variants of lung	12.31	12.25	12.36	192,771	62,439	5.9	13.7	14.1	121,904
	Adenocarcinoma with variants of lung	11.63	11.58	11.68	182,175	59,007	40.4	15.9	16.3	866
	Poorly differentiated endocrine carcinoma of lung	7.91	7.86	7.95	123,888	40,128	17.5	5.7	6.0	3,183
Female genital common tumours		74.17	74.03	74.30	1,161,864	394,087	**82.20**	82.10	82.30	1,131,902
	EPITHELIAL TUMOURS OF BREAST	63.52	63.40	63.65	995,119	318,878	82.4	82.3	82.5	971,037
	Invasive ductal carcinoma of breast	46.56	46.45	46.66	729,345	236,237	85.4	85.3	85.6	723,998
	Invasive lobular carcinoma of breast	7.75	7.71	7.80	121,455	39,340	86.2	85.9	86.5	120,973
	EPITHELIAL TUMOURS OF CORPUS UTERI	10.64	10.59	10.70	166,745	75,209	81.2	80.9	81.4	164,787
	Adenocarcinoma with variants of corpus uteri	9.93	9.88	9.98	155,550	50,383	83.0	82.7	83.2	154,968

Male genital and urogenital common tumours		85.27	85.13	85.42	1,335,876	462,665	**75.90**	75.80	76.00	1,277,743
	EPITHELIAL TUMOURS OF PROSTATE	55.06	54.95	55.18	862,576	301,113	84.0	83.8	84.1	842,467
	Adenocarcinoma with variants of prostate	48.86	48.75	48.97	765,405	247,917	88.1	88.0	88.3	762,360
	EPITELIAL TUMOURS OF KIDNEY	12.66	12.61	12.72	198,402	65,848	60.5	60.2	60.7	187,324
	Renal cell carcinoma with variants	10.08	10.03	10.13	157,886	51,140	68.5	68.2	68.8	153,460
	EPITHELIAL TUMOURS OF BLADDER	17.55	17.48	17.61	274,896	95,704	60.4	60.1	60.6	266,941
3	Transitional cell carcinoma of bladder	15.68	15.62	15.74	245,681	79,577	62.7	62.4	63.0	243,620
Common skin tumours and non-cutaneous melanoma		69.08	68.95	69.21	1,082,244	350,542	**95.60**	95.50	95.70	1,048,046
	MALIGNANT SKIN MELANOMA	14.06	14.00	14.12	220,206	71,325	83.8	83.6	84.0	216317
	Malignant skin melanoma	14.06	14.00	14.12	220,206	71,325	83.8	83.6	84.1	216,317
	EPITHELIAL TUMOURS OF SKIN	55.03	54.91	55.14	862,038	279,217	98.8	98.7	99	837,895
	Basal cell carcinoma of skin	40.75	40.65	40.85	638,347	206,763	101.6	101.5	101.8	634,953
	Squamous cell carcinoma with variants of skin	14.28	14.22	14.34	223,691	72,454	89.7	89.4	90.1	221,487
Haematological common malignancies		11.03	10.98	11.08	172,794	58,286	60.5	60.2	60.8	166,040
	LYMPHOID DISEASES	**11.03**	10.98	11.08	**172794**	**58286**	**60.5**	60.2	60.8	**166040**
	Other non Hodgkin, Mature B cell lymphoma	6.37	6.33	6.41	99,729	32,303	68.3	67.8	68.7	97,389
All common tumours	**ALL COMMON**	384.37	384.07	384.68	6,021,483	**2,036,963**	**63.4**	63.3	63.4	**5633710**

Note: the first tier entities (capital letters) are not a sum of the second tiers (small letters) included because of the NOS entities

Table 2. Age standardized incidence in 1999-2002 and 2003-2007, and corresponding Annual Percent Changes (APC) between the two periods, of rare cancers lying outside the 3-standard-errors confidence bounds in Figure

~~**Table 2. Variations over time in age adjusted incidence rates of rare cancers lying outside the confidence bounds in Figure 1**~~

Cancer entity	1999-2002	2003-2007	APC	Confidence limits	
Gastrointestinal stromal sarcoma	0.098	0.258	24.1	12.0	36.2
GEP, Poorly differentiated endocrine carcinoma of pancreas and digestive system	0.361	0.618	12.7	7.7	17.8
Other T cell lymphomas and NK cell neoplasms	0.395	0.555	7.8	3.3	12.4
Diffuse B lymphoma	2.837	3.894	7.3	5.7	8.9
Other myeloproliferative neoplasms	1.530	2.092	7.2	5.0	9.4
Mantle cell lymphoma	0.367	0.477	6.0	1.6	10.4
Carcinomas of thyroid gland	3.470	4.353	5.2	3.7	6.6
Other myelodysplastic syndrome	1.395	1.738	5.0	3.0	7.1
Squamous cell carcinoma with variants of anal canal	0.595	0.728	4.6	1.2	8.0
Follicular B lymphoma	1.676	2.021	4.2	2.2	6.3
Cholangiocarcinoma of IBT	0.685	0.816	4.0	0.9	7.0
Neuroendocrine carcinoma of other sites	0.683	0.801	3.6	0.5	6.7
Adenocarcinoma with variants of oesophagus	2.725	3.153	3.3	1.8	4.8
Squamous cell carcinoma with variants of oropharynx	2.412	2.732	2.8	1.1	4.5
Adenocarcinoma with variants of EBT	0.969	1.088	2.6	0.1	5.1
Hepatocellular carcinoma of Liver and IBT	2.068	2.273	2.1	0.4	3.8
Squamous cell carcinoma with variants of cervix uteri	4.536	4.287	-1.2	-2.4	-0.1
Adenocarcinoma with variants of ovary	5.351	5.053	-1.3	-2.3	-0.2
Squamous cell carcinoma with variants of larynx	3.853	3.578	-1.6	-2.8	-0.4
Chronic myeloid leukemia	0.991	0.854	-3.2	-5.5	-0.9
Infiltrating duct carcinoma of prostate	0.412	0.343	-4.0	-7.4	-0.6
Squamous cell carcinoma with variants of lip	0.838	0.693	-4.1	-6.5	-1.8
Large cell carcinoma of lung	3.440	2.806	-4.4	-5.6	-3.2
Mucinous adenocarcinoma of ovary	0.813	0.657	-4.6	-7.2	-2.1
Adenocarcinoma with variants of bladder	0.265	0.213	-4.7	-8.9	-0.5
Undifferentiated carcinoma of stomach	0.189	0.123	-9.2	-13.9	-4.5

~~Table 3. Variations over time in age adjusted 5-year relative survival of rare cancers lying outside the confidence bounds in Figure 2~~

Table 3. Age standardized 5-year relative survival in 1999-2001 and 2005-2007, and corresponding difference between the two periods, of rare cancers lying outside the 3-standard-errors confidence bounds in Figure 1

Entity	1999-2001 5-year surv	2005-2007 5-year surv	Difference	lower	upper
Chronic myeloid leukemia	37.2	57.9	20.7	17.4	24.1
Infiltrating duct carcinoma of prostate	67.5	79.8	12.3	6.4	18.2
Soft tissue sarcoma of viscera	34.7	43.7	9.0	3.6	14.4
Kaposi's sarcoma	75.4	84.2	8.8	1.4	16.2
Diffuse B lymphoma	46.9	55.2	8.4	6.5	10.2
Follicular B lymphoma	69.5	77.9	8.4	5.9	10.8
GEP, Poorly differentiated endocrine carcinoma of pancreas and digestive system	25.3	32.7	7.5	2.7	12.2
Squamous cell carcinoma with variants of oropharynx	37.5	44.5	7.1	5.0	9.2
Soft tissue sarcoma of superficial trunk	43.9	50.4	6.5	1.4	11.6
Precursor B/T lymphoblastic leukemia/lymphoma (and Burkitt leukemia/lymphoma)	54.3	60.8	6.4	3.8	9.1
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	29.8	35.0	5.2	3.8	6.7
Carcinomas of thyroid gland	85.6	90.6	5.0	3.8	6.3
Adenocarcinoma with variants of cervix uteri	63.8	68.8	5.0	1.7	8.3
GEP, Well differentiated not functing endocrine carcinoma of pancreas and digestive system	67.7	72.6	4.9	1.5	8.4
Soft tissue sarcoma of limbs	63.9	68.4	4.4	1.0	7.9
Adenocarcinoma with variants of oesophagus	9.9	13.8	3.9	2.6	5.1
Squamous cell carcinoma with variants of oral cavity	46.1	49.7	3.7	1.7	5.6
Squamous cell carcinoma with variants of hypopharynx	22.2	25.6	3.4	0.5	6.3
Other myeloproliferative neoplasms	70.8	74.0	3.2	0.6	5.9
Squamous cell carcinoma with variants of cervix uteri	65.1	68.1	3.0	1.6	4.5
Large cell carcinoma of lung	10.9	13.6	2.7	1.6	3.9
Adenocarcinoma with variants of EBT	16.2	18.7	2.6	0.2	5.0
Squamous cell carcinoma with variants of oesophagus	9.5	12.0	2.5	1.3	3.7
Hepatocellular carcinoma of Liver and IBT	11.0	13.0	2.0	0.5	3.5
Other myelodysplastic syndrome	33.8	30.2	-3.5	-6.3	-0.8

Table 4. Annual number of cases, number of hospitals providing 75% of treatments (H75), mean annual number of treatments (treat) provided by H75 hospitals, by country and cancer group

Group	Country, population (millions)																				
	Belgium (10.5)			Bulgaria (7.7)			Finland (5.3)			Ireland (4.2)			Netherlands (16.3)			Slovenia (2.0)			Navarra (0.6)		
	cases	H75	treat	cases	H75	treat	cases	H75	treat	cases	H75	treat	cases	H75	treat	cases	H75	treat	cases	H75	treat
Haed & Neck	2,098	29	105.6	1,180	10	145.1	439	6	82.2	368	7	63.0	2,439	12	201.4	395	2	266.1	125	2	76.6
Epithelial Ovary	760	50	19.5	627	16	52.3	370	10	44.5	261	15	21.0	1,118	47	30.2	158	3	82.0	38	1	45.5
Oesophagus	689	31	29.3	77	14	5.2	163	8	21.6	289	9	37.1	1,422	31	42.0	49	2	32.9	24	2	15.7
Central Nervous System	623	20	48.4	412	13	41.7	57	4	19.1	229	3	106.3	912	14	84.0	97	2	78.7	47	2	32.0
Soft Tissue Sarcoma	500	35	16.6	372	21	18.4	165	7	25.6	157	17	10.6	802	33	26.4	81	2	47.4	32	2	17.4
Thyroid	576	34	14.2	220	12	20.4	286	12	22.8	98	11	9.6	418	31	17.1	109	1	260.3	43	2	36.8
Testis	244	40	8.4	180	19	12.4	101	9	14.3	144	12	15.6	609	42	18.4	93	3	48.8	10	3	4.4
Biliary Tract	214	44	4.9	183	23	6.5	147	13	11.3	122	14	7.7	582	38	12.2	47	3	13.2	43	2	19.7
GEP	287	46	5.6	30	21	1.3	148	13	9.3	61	20	2.7	355	44	6.9	22	3	6.8	10	3	2.9
Liver	250	22	11.0	107	12	7.6	165	11	12.8	68	12	4.6	236	36	5.2	29	2	14.4	49	3	14.5
Urinary Tract	292	48	6.7	67	17	4.1	48	12	3.9	24	10	2.3	419	46	7.7	30	3	8.9	19	3	8.2
Mesothelioma	184	25	8.7	34	10	3.7	64	9	6.8	25	11	2.0	481	43	9.8	21	1	22.3	9	2	4.6
Vagina	172	35	5.8	120	9	14.0	70	5	14.8	40	9	4.7	296	14	21.8	42	2	21.9	8	2	4.7
Bone Sarcoma	81	10	10.2	55	13	4.6	28	3	9.6	30	7	5.2	195	5	43.3	15	2	10.4	3	2	2.4
Anal Canal	95	27	5.3	39	12	4.1	24	7	4.6	30	9	4.4	135	22	7.2	15	1	23.6	4	2	3.6
Melanoma of uvea	43	2	21.9	17	7	2.7	6	1	5.5	29	4	5.7	156	2	80.2	13	1	11.9	3	3	0.8
Penis	63	43	1.4	39	17	2.4	21	10	2.1	20	15	1.2	109	26	3.7	9	4	2.0	4	3	1.2
Small Intestine	62	37	1.9	15	13	1.1	26	13	2.1	27	20	1.3	120	38	2.6	5	4	1.3	2	2	1.0
Neuroendocrine carcinoma of skin	46	32	1.9	1	3	0.4	0			15	18	0.8	77	37	2.3	4	4	1.1	0		
Non epithelial Ovary	20	19	1.3	43	17	3.2	8	9	1.1	8	15	0.6	32	24	1.4	4	3	1.7	1	3	0.3
Endocrine carcinoma of thyroid	31	22	1.4	10	9	1.2	8	8	1.2	5	10	0.5	32	13	2.7	5	1	10.3	1	1	1.7
Thymus	22	20	1.4	7	8	1.3	4	5	1.1	5	5	1.3	36	15	2.8	3	2	2.1	2	2	1.3
Nephroblastoma	18	4	7.4	6	3	2.8	8	3	4.7	7	1	13.4	30	4	16.9	3	1	4.8	0	1	0.3
Melanoma of mucosa	14	24	0.8	2	5	0.8	10	7	1.7	6	11	0.6	34	13	3.0	4	3	1.5	1	2	0.3
Adrenal cortex	13	14	1.1	13	10	1.3	6	7	0.9	5	11	0.4	25	15	1.5	3	2	1.4	1	2	0.4
Embryonal CNS	21	9	4.2	14	9	2.5	6	3	3.1	9	3	6.3	0				2	4.2	2	1	5.2

Neuroblastoma	15	4	5.7	8	5	1.7	1	1	2.1	7	2	5.4	12	4	6.2	1	2	1.3	1	1	1.8
Retinoblastoma	10	1	14.0	3	5	0.5	3	2	1.5	3	2	1.8	22	1	30.7	1	1	1.1	1	2	0.5
Trachaea	10	18	0.9	5	4	1.1	4	5	0.9	2	4	0.4	11	11	1.1	3	1	3.8	1	1	0.5

Table S1. Annual number of cases observed, Expected Mean Admission Volume (MAV) level estimated and Estimated MAV indicator, by cancer, from the pool of the seven countries. Detailed estimated MAV indicator, by cancer and country

Group of cancer	Cases	Estimated MAV							
		POOL	Belgium	Bulgaria	Finland	Ireland	Netherlands	Slovenia	Navarra
Haed & Neck	6749	82.6	45.8	86.5	32.5	66.8	94.2	218.4	38.1
Epithelial Ovary	3102	20.0	10.6	30.3	17.7	11.3	12.8	62.2	16.2
Oesophagus	2168	23.0	17.0	3.7	8.8	37.5	27.2	22.7	4.6
Central Nervous System	2144	35.4	21.0	29.0	8.7	61.4	35.9	57.7	12.1
Soft Tissue Sarcoma	1968	11.9	9.6	11.1	11.3	7.1	15.4	19.2	6.3
Thyroid	1669	21.3	14.3	16.7	18.1	9.3	11.6	75.3	13.6
Testis	1369	13.3	4.6	7.4	7.2	10.9	10.4	46.9	2.2
Biliary Tract	838	6.4	4.7	6.2	5.3	2.6	7.8	14.5	7.2
Urinary Tract	816	4.1	3.5	3.8	2.1	1.4	4.6	10.3	3.7
GEP	763	4.2	4.0	1.1	6.7	1.3	3.8	5.7	1.5
Vagina	701	7.5	3.0	9.3	5.9	3.9	11.4	11.0	2.5
Liver	566	7.1	9.7	6.6	5.5	3.5	7.0	5.4	2.3
Mesothelioma	530	5.3	5.2	2.5	3.2	1.2	5.8	12.3	2.3
Bone Sarcoma	387	10.8	5.5	4.1	5.3	3.8	21.9	5.4	1.0
Anal Canal	322	4.2	2.7	2.3	2.0	4.5	5.7	9.2	1.2
Penis	254	4.0	1.0	1.8	1.1	0.9	10.4	2.7	1.0
Melanoma of uvea	245	21.1	12.4	1.8	4.5	3.1	39.5	6.9	0.6
Small Intestine	200	1.2	1.2	1.0	1.3	0.5	1.5	1.2	1.0
Neuroendocrine carcinoma of skin	135	1.0	0.9	0.3		0.7	1.3	0.9	
Non epithelial Ovary	113	1.1	0.8	2.0	0.5	0.4	0.9	1.1	0.2
Endocrine carcinoma of thyroid	87	1.4	1.2	0.9	0.7	0.4	1.6	4.0	0.6
Thymus	74	1.0	0.7	0.8	0.4	0.8	1.4	1.3	0.6
Nephroblastoma	71	4.0	3.3	1.8	1.6	6.1	5.9	2.1	0.2
Melanoma of mucosa	65	0.9	0.4	0.4	0.8	0.6	1.4	1.0	0.2
Embryonal CNS	55	2.3	1.6	1.6	1.0	4.4		2.6	1.5
Adrenal cortex	54	0.9	0.7	1.6	0.4	0.3	1.1	1.2	0.2
Neuroblastoma	43	2.2	1.8	1.7	0.6	3.6	2.3	0.7	0.7

Retinoblastoma	41	7.7	4.9	0.4	1.3	2.2	14.8	0.7	0.2
Trachaea	33	0.8	0.4	1.0	0.4	0.4	0.8	2.1	0.3
Eye	21	0.7	0.3	0.7	0.1	0.3	1.1	0.9	0.4
Olfactory Neuroblastoma	17	0.5	0.5	0.7	0.4	0.2	0.7	0.3	
Placenta	14	0.4	0.3	0.4	0.2	0.1	0.5	0.1	0.2
Hepatoblastoma	10	1.0	0.6	0.5	0.3	1.5	1.2	0.4	
Middle ear	10	0.4	0.4	0.6	0.2	0.3	0.5	0.1	
Parathyroid	9	0.3	0.3	0.5	0.3	0.2	0.5	0.1	0.2
Pituitary	3	0.2	0.3		0.3	0.2	0.3		
Parcreatoblastoma	1	0.3		0.3					
Pleuropulmonary blastoma	0	0.2			0.1		0.3		

Manuscript reference number: THELANCETONCOLOGY-D-17-00424

Title: Burden, time trends and centralized treatment of rare tumors: a European perspective. The RARECAREnet Project

Replies to Reviewer 1

This is a very interesting study addressing the incidence or rare cancers in EU, by pooling together the data from cancer registries collected in 90' and 00'. This represents a follow-up of a previous effort, by an experienced group, with addition information on evolution of incidence and 5-year survival. The limits of the methods are described and carefully considered . The results are of importance at the time of the ERN as rightly pointed out. The following points need to be addressed to improve the quality of the manuscript.

Major points:

1. I noted imprecisions and non-consistent data in the first tables. For instance, the incidence of gastrointestinal stromal sarcoma (GIST) is 0.30, notably inferior to what is known now. There may be overlaps between organ based classification (eg gyne) and histologies (NET, sarcoma; eg : getting back to the same example, are gist also present in visceral sarcoma?

Replay: It is true, incidence of GIST is underestimated. This was recognized in several papers studying GIST from population-based data. The new ICD-O code of GIST was at the beginning underused by pathologists. However, its use is increasing, as suggested by the growing trend (Fig and Table).We can mainly attribute the rising incidence trend for GIST to the introduction of the new code and to its rising use in Europe. Now, we have stressed more the point in the discussion, page14. There is no overlapping use of ICD-O codes in our rare cancers classification, thus GIST is not included in visceral sarcoma, nor NET in epithelial tumours, and so on.

2. The writing is often technical for a mostly oncology reader. For instance, to which extent DCO, MAV are commonly used criteria in other published experience. This could be improved relatively easily.

Replay: We tried to remove throughout the manuscript all the unnecessary technicalities. In particular, we tried to make more clear the use of the MAV indicator that, to our knowledge, has been for the first time used in this work.

3. A more precise discussion on what should be done to monitor better incidence and 5-year survival rate, in the discussion section would be very useful.

Replay: We expanded this issue in the discussion (page 20).

4. More detailed legends would be useful for the figures
Replay: we have improved them.

Minor points

1. The discussion could be condensed and shortened.

Replay: we little shortened the discussion.

Reviewer #2: General comments

Much of what is presented here simply updates and refreshes these authors' previous publication in the European Journal of Cancer. What is novel is the attempt to estimate the extent to which, in different jurisdictions, the treatment of rare cancers is centralised. This is an important contribution to our knowledge concerning how best to organise cancer services and will, in the future, prove useful in assessing the effects of increased or decreased centralisation on outcomes for patients with rare cancers.
Replay: We agree, and we also provided for the first time incidence and survival trends. We intended to provide a baseline analysis relevant to the European efforts on rare cancers with the Joint Action and the European Reference Network.

Nearly one quarter of all cancers in Europe are rare cancers: the definition used here is of 6/100,000. Others have used absolute prevalence of 200,000 (FDA) or <15/100,000 (Greenlee et al 2010). Estimates of rare cancer incidence will depend critically on the criteria used for lumping and splitting within the ICDO classification. If head and neck cancer were to be considered as a group of tumours, rather than as 17 separate entities, then its incidence rate at 18.2/100,000 is well above any of these thresholds.

Replay: In the US, the American Cancer Society adopted our cut off for its recent report https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html. The same was for the Japanese and other European countries papers.

Actually, epithelial H&N tumours are considered as both a single broad family including, 17 clinically distinct rare entities. This example is now better clarified at page 10. This point addresses the structure of rare cancers classification. The first paragraph added to the Method section refers to the relevant sources describing rationale and structure of our classification. We think this could be sufficient for documentation, and would avoid a long additional paragraph in the present article (Page 9)

Centralisation & Expertise

1. I suspect that the figures for mean annual hospital volume are highly skewed (no data shown). This calls into question the use of means, rather than medians, in the analysis. This potential objection is probably answered by their use of regionally-based mean admission volume as the metric of interest. The mean admission volume is effectively a weighted average, and this approach should compensate for any difficulties imposed by unequal distributions of activity at the level of the individual centres. Perhaps this advantage of their approach needs to be made more explicit.

Replay. The reviewer is right: the volume distribution among hospitals is highly left-skewed because many hospitals have low volume and very few have high volumes. When considered among patients, the volume distribution is much less skewed because many patients are treated in those few high volume hospitals. According to our definition, MAV can be also interpreted as the mean of hospital specific volumes weighted by the number of patients treated. As a consequence, the median admission volume over all patients for a given cancer/country combination is not too different from the orresponding mean admission volume (MAV) mostly ranging within 0.7-1.2. Correlation between mean and median admission volumes over all the entities is between 0.97 and 0.99 for all countries, so they basically provide the same information. We added a sentence at the last paragraph of the Methods section, Page 10.

2. The mean admission volume estimates will, to a considerable extent, depend upon how specialist cancer services are organised. If a biopsy is performed at one hospital, then the patient is referred to another hospital for specialist surgery, and then to a third hospital for radiotherapy and chemotherapy, then the activity per hospital will be low. If, however, the separate hospitals are grouped administratively as a single cancer centre or network then the unit activity will be correspondingly higher. The authors' approach is, therefore, sensitive to the way in which cancer services are organised, perhaps this is something that ought to be more fully acknowledged as a potential limitation to their approach.

Reply. We accept the comment and modified accordingly a paragraph of the discussion at page 16

3. The approach used in their analysis would not identify patients being treated across various centres using common protocols. You cannot assume therefore that there is a direct correlation between access to optimal treatment and number of treatments per centre per year.

Reply: we partly agree with, registries are not able to reach the information whether a patient is or not treated according to an agreed protocol, mainly because this information is rarely reported in the clinical record. What we would like to stress is that a high number of diagnosed and treated patients, can provide a sound expertise and help to a better application of agreed protocols. This is mainly true for complex surgery, but also for high technology radiotherapy or for general management of complex patients. However, we are not able to demonstrate that patients with rare cancers are more appropriately cured in high volume hospital. Our aim is to address the centralization issues and we hope that this is more clear in the reviewed discussion (page 16).

4. Expertise and numerical activity may not be tightly related. The development of the total mesorectal excision for rectal cancer, pioneered at Basingstoke, is a good example of how a centre that is small - in terms of patients treated per annum - can innovate and generate outcomes that are superior to those achieved in busier centres.

Reply: we recognise the brilliant example of mesorectal excision. However, this exception may be more applicable to a common cancer, like rectal cancer, for which a critical number of surgically treated cases can be reached by a small center.

5. The attractant properties of specific technologies lead to increased localisation of services. It is

therefore not surprising that thyroid cancer and sarcomas have higher mean admission volumes than would be expected from their incidence, as emerges from the rankings in table S1. The management of thyroid cancer requires specialist nuclear medicine facilities and the management of sarcoma is critically dependent upon advanced techniques both in surgery and in rehabilitation.

Reply: We agree that for STS and thyroid specific technologies should lead to increased localisation of services. Actually, we observed higher MAV than expected for thyroid and for bone, but not for soft tissues sarcomas.(page 13).

6. A recent paper from Korea (Shin DW, Cho J, Yang HK, Kim SY, Lee SH, Suh B, et al. Oncologist Perspectives on Rare Cancer Care: A Nationwide Survey. Cancer Res Treat. 2015;47(4):591-9) outlines oncologists' views of the problems they encounter in the management of rare tumours. It also hints at the potential difficulties that might arise when attempts are made to centralise services for patients with rare tumours.
Reply: We knew the interesting paper reported by the reviewer; we are aware that centralization is sometimes not perceived as a the ideal solution therefore we include this point of view in the discussion (page17). We added a new reference..

Pathology and Registration

7. The analysis relies on the pathology of up to 20 years ago, and may be of questionable relevance to future practice, which will be increasingly based on molecular and genomic classification.

Reply: we included in the Discussion (Page 20) the point raised by the reviewer.

8. The rise in incidence for gastrointestinal stromal tumours is probably an example of ascertainment bias. Once you start performing immune staining for mutant c-kit, then the incidence rises. The authors need to discuss the molecular and genetic phenotyping of individual tumours and how this will have an impact on the estimates of the incidence of rare tumours and how this might cause fragmentation of apparently homogeneous categories. The overall effect would be to decrease the number of patients per category.

Reply: we completely agreed with the reviewer with the example of GIST. In this case the ICD-O included a new code and GIST started to be identified by cancer registries. Other new codes, because of new tests, mainly for the haematologic group of neoplasms, were included in the ICD-O. In our proposed list, the new entities were not recognised as specific rare entities, because they were grouped with other rare entities sharing the same therapeutic approach and expertise, see the group of acute myeloid leukaemia. The statement included in the discussion (page 20) can answer the question raised by the reviewer.

9. A flow diagram (or Venn diagram) indicating which registries contributed to which aspects of this study would have been very helpful.

Reply: We do not think this request add more information that what was reported in the Material and Method section.

10. I was unable to obtain access to the cited reference in Tumori (2017) but note that questions have been raised concerning the quality of data from registries in Eastern and Southern Europe (Rare Cancers Europe Survey 2012.

Reply: We attach a *pdf* version of the *Tumori* paper, for reviewer's consideration. We do not know the Rare Cancer Europe Survey 2012, but we don't completely agree with this statement. The study, published in *Tumori*, included data also from Sweden, Ireland, Austria, Belgium, Netherlands, Austria, Switzerland and France and no major quality differences were found between registries from different European regions.

Minor points

11. A brief description of the Ederer-2 method would be helpful (the reference provided is unobtainable)

Reply: we provide an alternative citation for relative survival estimation

Ederer F, Axtell LM, Cutler SJ. The relative survival: a statistical methodology. Natl Cancer Inst Monogr 1961; 6: 101–21.

12. I'm not convinced that Kaposi's sarcoma should be included with the other sarcomas. It is a virally related tumour, it responds to highly active retroviral therapy and it is this factor that has probably had the main impact on improving survival from Kaposi's sarcoma.

Reply: We agree. Actually, Kaposi's sarcoma **did not** contribute to the incidence and survival rates of sarcomas,. It is a separate rare entity.

13. The sentence on page 13 "centralisation of epithelial ovarian cancers was not slow in Bulgaria and Slovenia" is a little difficult to understand. Perhaps it could be rewritten as "in Bulgaria and Slovenia the management of epithelial ovarian cancers was highly centralised."

Reply: Thanks. We have re written the sentence as suggested.

14. On page 14 there is the statement "the drop in incidence for some of the rare cancers was due to the still falling prevalence of smoking". The reference given (16) is to smoking prevalence itself rather than to the effects of smoking on the incidence of rare cancers.

Reply: we provided a more precise reference, WHO, THE EUROPEAN TOBACCO CONTROL REPORT 2007, http://www.euro.who.int/__data/assets/pdf_file/0005/68117/E89842.pdf

15. I did not have access to the figure captions: the use of a log scale for the X-axis in Figure 3 deserves specific comment.

Reply: we added a comment at page 12 and of course we will pay attention to correctly include figure captions.

16. Reference 27 in the text is reference 25 in the bibliography (there is no reference 27)

Reply: We corrected the reference

17. P15 "like for incidence" - sentence needs rewriting
Reply: we rewrited the sentence

Reviewer #3: First rate study. As a consequence I have little of substance to add. My comments are below.

1. Table 2. I assume 95% confidence limits.

2. Table 3. Lower and upper what? I assume 5-year survival is a percentage.

Reply: Following the standard practice in presenting funnel plot analysis with a large number of statistical units, confidence bound correspond to plus or minus three standard deviations from the zero change, corresponding to 99.8% confidence limits. We gave more details in titles of both Tables 2 and 3

3. Abstract. If space permits a sentence of what constitutes a rare cancer to be included.

Reply: we have included the information requested .

4. Is death all-cause?
Reply: yes, relative survival analysis considers death for all causes, corrected by general population mortality rates to eliminate expected deaths not due to cancer (details in references 4 and 7).

5. Given the quality of data there's no reason as to why sex-specific incidence (overall, not by country) couldn't be provided

Reply: we accepted the suggestion and a Supplementary Table is attached

6. Provide a STROBE Statement.

Reply: we do not understand this point

Final review:

My overall comment is that the data are per se interesting, but not particularly new and add to a limited amount to what we know and what should be done.
The part about management is purely ecological and any projections about what type/degree etc of centralisation of care is needed to achieve results remain speculative. Hospital volume is also a moving target and much has happened since 2007.
Reply: as far as we know, cancer survival and incidence trends are rarely given. Furthermore, we think that our contribution answers to the increasing interest of the EC expressed by the Joint action on Rare Cancers and the ERN. Therefore, as stated, this 'old' picture will help the evaluation of activities on rare cancers at European and country level.

Editorial comments

1. Please confirm that all authors who qualify for authorship for this manuscript (in adherence with ICMJE guidelines) are included in the authorship.

Replay: Confirm

2. Please confirm that all individuals who need to be acknowledged in this manuscript are in the Acknowledgments section.

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Replay: the research was funded only by the EC.

***Reply to Reviewers Comments**

Manuscript reference number: THELANCETONCOLOGY-D-17-00424
Title: **Burden, time trends and centralized treatment of rare tumors: a European perspective. The RARECAREnet Project**

Second revision

1. Please check with your co-authors, and confirm, that all names are spelt correctly, and affiliations listed correctly. We cannot guarantee that we will be able to correct names and affiliations after publication of your article.
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2. The study title should have a descriptor—ie, randomised trial, case-control study, prospective analysis, population-based study etc…
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3. Please supply (after author names on the title page) one preferred degree per author and indicate in the authorship if any authors are full professors.
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4. Please give full first names for all authors.
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5. Summary: Your abstract should conform to the CONSORT guidelines for abstracts (CONSORT for Abstracts: Lancet 2008; 371: 281-83), and must include:

   a) Background: A sentence indicating the aim of this study.
   b) Methods: A brief summary of the main patient characteristics (ie, main entry criteria)
   c) Interpretation: please do not just restate your findings. What do they mean, clinically? What are their implications?
   d) A line at the end of the abstract stating who funded the research.

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6. Please confirm that your study conforms to the STROBE guidelines by completing and returning the checklist.

   STROBE - Observational studies — http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61602-X/fulltext

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   Reply: done (see pages 7 and 8)

7. If you have included such data for a drug(s), please confirm that the dose, route, and frequency of administration (and the form: eg, a particular salt) are correct.

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9. Please do not translate HRs/RRs/ORs into percentages, since this can be misleading. Simply indicate the HRs/ORs/RRs and let the reader interpret the data.

10. Lancet style is to provide p values to 2 significant figures, unless p<0.0001 (if this is the case, then please revise to the latter).

Reply: from point 7 to 10, not applicable

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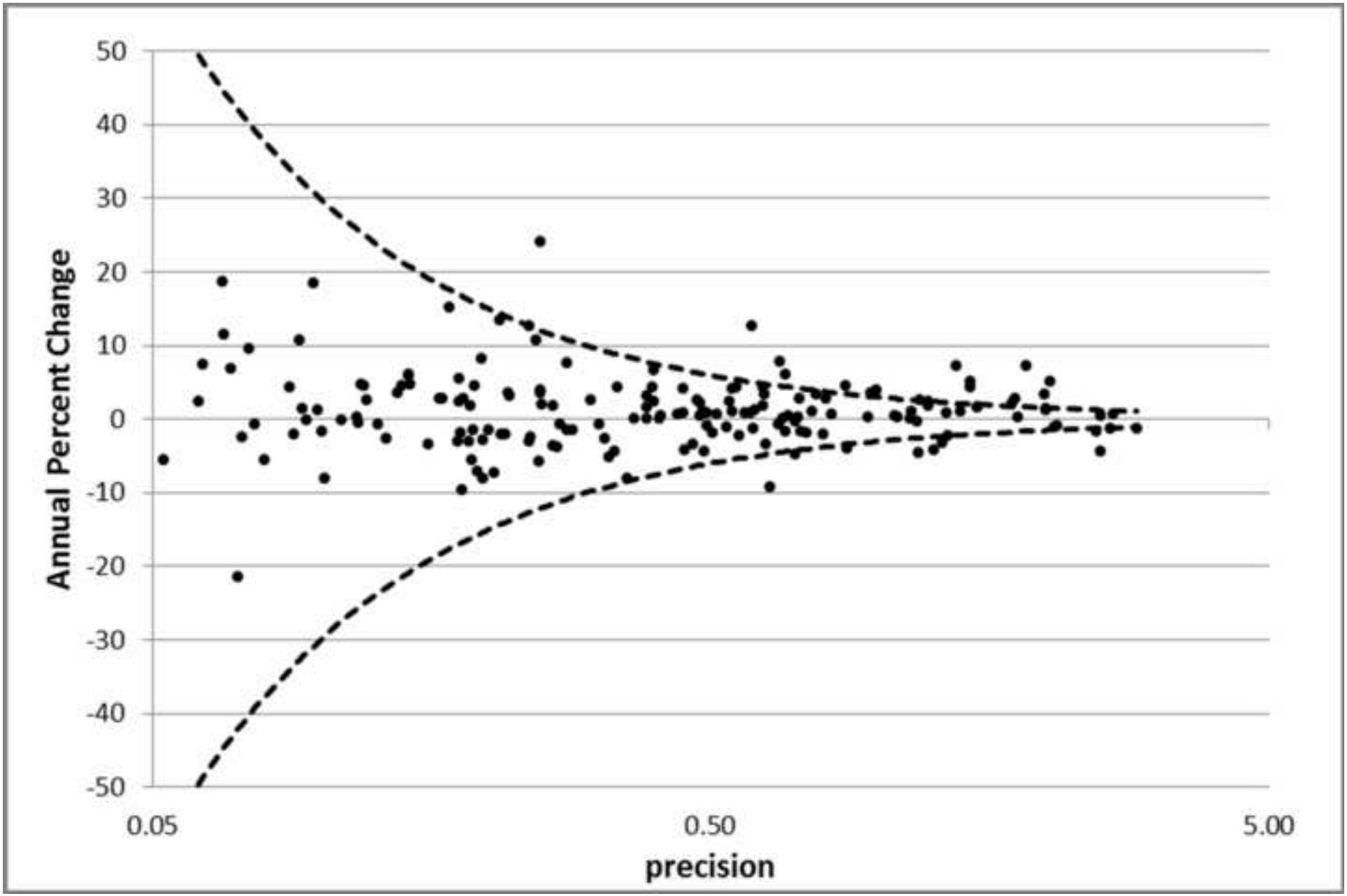

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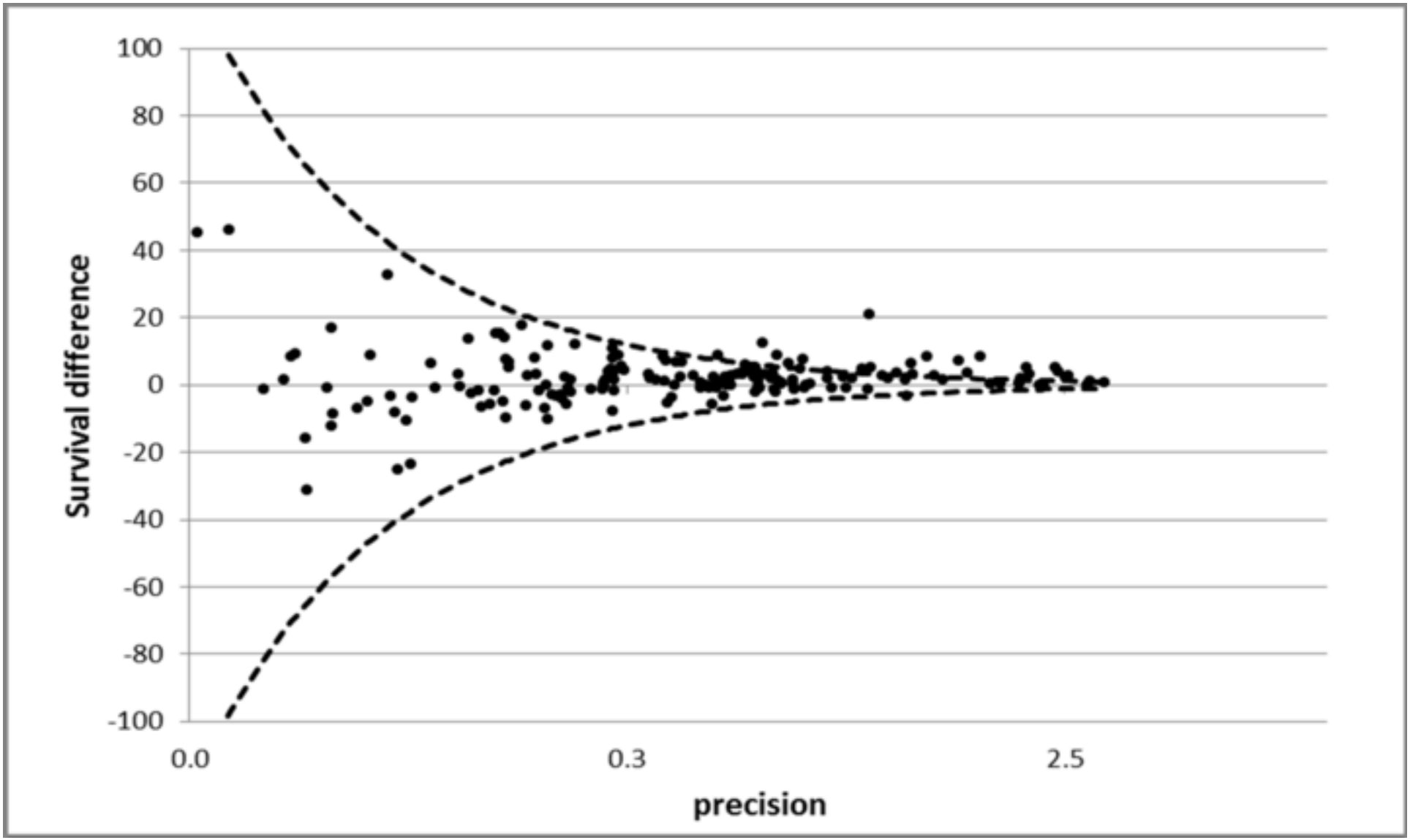

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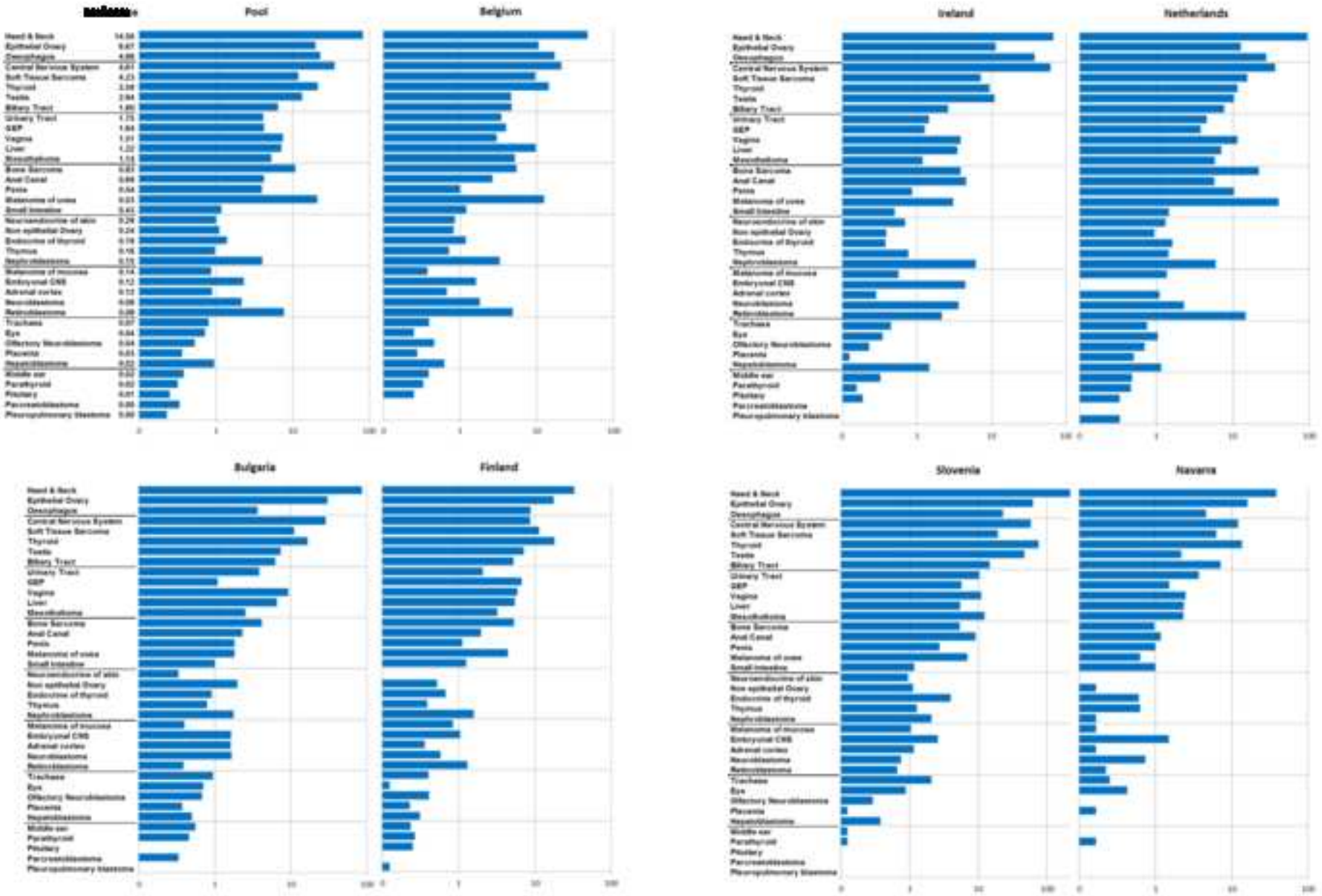

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